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## CONTENTS

The Frank E. Bunts Institute ... 3

Infections of the Middle Ear
*Paul M. Moore, Jr., M. D., Department of Otolaryngology* ... 5

The Diagnostic Significance of an Increased Q-T Interval in the Electrocardiogram
*Charles P. Wofford, M. D., Fellow in Medicine, and A. Carlton Ernstene, M. D., Section on Cardiorespiratory Diseases* ... 12

Proctoscopic Observations in Gastro-Intestinal Allergy; Report of Two Cases
*J. Warrick Thomas, M. D., Department of Allergy, and R. John F. Renshaw, M. D., Section on Gastro-Intestinal Diseases* ... 17

Report of a Case of Hyperthyroidism
*E. J. Ryan, M. D., Special Fellow, Section on Endocrine and Metabolic Diseases* ... 21

The Nephrotic Syndrome
*R. H. McDonald, M. D., Section on General Medicine* ... 27

Stilbestrol in the Treatment of Ovarian Deficiency
*E. Perry McCullagh, M. D., Section on Endocrine and Metabolic Diseases, and T. Reid Jones, M. D., Fellow in Medicine* ... 32

Neurocirculatory Asthenia
*C. L. Hartsock, M. D., Section on General Medicine* ... 42

Recent Developments Resulting in an Increasing Operability Rate for Cancer of the Stomach
*George Crile, Jr., M. D., Department of Surgery* ... 50

Uveitis
*A. D. Ruedemann, M. D., Department of Ophthalmology* ... 58

The Frank E. Bunts Institute
*Program of Course in Diseases of the Heart, Circulation, and Kidneys* ... 63

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# THE FRANK E. BUNTS INSTITUTE

announces

## A Graduate Review Course

in

## Diseases of the Heart, Circulation, and Kidneys

on

**MONDAY, TUESDAY, and WEDNESDAY**
**MARCH 24, 25, and 26, 1941**

The fee for the course will be ten dollars ($10.00). Registration will be limited to one hundred doctors who are graduates of accredited medical colleges. Because of the interest which has been shown in the previous courses, it is desirable that applications be sent as early as possible in order that provisions may be made to accommodate the maximum number who desire to attend.

Further information may be secured from A. D. Ruedemann, M.D., Chairman, Frank E. Bunts Institute, Cleveland Clinic, Cleveland, Ohio.

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**A description of the course and an outline of the subjects to be covered will be found on pages 63 and 64.**

# INFECTIONS OF THE MIDDLE EAR

PAUL M. MOORE, JR., M.D.

In infections of the ear, it is well to bear in mind the mechanical features of the eustachian tube, tympanum and mastoid. The system consists of connecting air chambers of varying sizes and shapes with a blind end in the mastoid and an open end in the nasopharynx. The normal physiology of the ear depends upon this mechanism remaining intact. The eustachian tube and adjacent portions of the tympanum are lined with ciliated epithelium which sweeps secretions down into the nasopharynx. The tube is constructed to open upon yawning and swallowing, and, in this manner, maintains the air pressure at the proper level in the middle ear.

Once infection invades this mechanism its normal function becomes impaired. At the orifice in the nasopharynx, at the junction of the cartilagenous and bony portions of the eustachian tube, and at the additus ad antrum which connects the middle ear and mastoid antrum are strategic points where barricades may be erected by nature to prevent the further invasion of the infection. We must determine in each case, (1) how far the invasion has progressed, and (2) how to prevent further spread of the infection. When the infection passes a barricade, that barricade becomes an obstacle to recovery because it blocks the drainage of pus back into the nasopharynx.

The first line of defense is at the opening of the eustachian tube into the nasopharynx. Here the normal secretions of the nose are swept above and below the opening by the ciliated epithelium of the nose and nasopharynx. If infection gains access to the nasopharynx and pus accumulates around the tubal opening, the tissues in the region become edematous and tend to close off this opening. The symptoms vary from referred pain and momentary stuffiness in the ears to a definite mild impairment of hearing, depending upon the severity of the infection and the amount of edema.

Treatment at this stage should be directed to the nose and nasopharynx. The nasal passages should be opened and kept open by the use of cocaine solutions or ephedrine. In the early serous stage the oily solutions are preferred because of the protection the oil gives the raw mucous membranes. The nasopharynx should be painted with 10 to 20 per cent argyrol or some other mild antiseptic solution. The argyrol should not be more than a week old, because after a week it undergoes disintegration and may be extremely irritating. If argyrol is prescribed for the patient to use himself, he should be warned against its continued use over a long period of time. Too many cases of argyrosis from continued self-medication with argyrol have been reported recently.

The continued use of ephedrine solutions also should be discouraged. Many patients develop a sensitization to ephedrine after long or very frequent use. The turbinates and septal mucosa become very swollen and pale, and there is marked nasal obstruction which is no longer relieved by ephedrine.

If the infection gains access to the lower end of the tube, a barricade is erected at the junction of the cartilagenous and bony portions. Because the tube is narrower here and the mucosa is in folds, very little edema of the tissues is required to close off this portion completely. At first the pain in the ear is somewhat more marked and the stuffiness more pronounced. In the early stages the drum still may have a normal color and lustre, and may show only some retraction. If the obstruction becomes complete and lasts long enough, some injection may appear around the rim of the drum; the air in the middle ear cavity may become absorbed and be replaced by a serous transudate. At this stage, an acute serous otitis media develops. The drum still is quite transparent and one may see a fluid level with air above.

As long as there is no bulging of the drum to indicate increased pressure within the middle ear, treatment should be directed toward the nose and nasopharynx. The application of 20 per cent argyrol directly to the eustachian tube openings in the nasopharynx often is very helpful and will tend to open up the lower end of the tube and to draw the secretions down out of it. The application of argyrol can best be accomplished by passing a curved probe, tipped with cotton, through the nose in the same way that one uses the eustachian catheter. This should be left in place for about five minutes.

Under no circumstances should the tubes be inflated in the presence of an acute infection. Such a procedure would only result in blowing infected material through nature's barricade into the middle ear. After all acute inflammation has subsided, inflations should be used to promote drainage and to restore normal ventilation. When fluid appears in the middle ear and is not under pressure, a 5 per cent solution of phenol in glycerine or auralgan will be very helpful if dropped into the external canal and allowed to remain in contact with the drum for five to ten minutes. This tends to ease the pain and to promote osmosis of the serum through the drum. If there is a definite bulging of the drum, a myringotomy should be done immediately. Increased pressure within the tympanum should be avoided if possible because if it is not relieved, it will cause some devitalization of the tissues. It also may spill over into the mastoid cells and produce a further extension of the infection.

When the actual infection breaks through the barrier in the eustachian tube, it progresses rapidly into the middle ear. There usually is a rise in temperature and in the leukocyte count. The pain may be quite severe

and persistent. The deafness is more marked and of the conductive type. The drum is edematous, thickened, and injected. The landmarks become obliterated and as the pressure within the middle ear increases, the drum bulges. At this stage a myringotomy should be done. Care should be taken to incise the drum down to the floor to allow an adequate opening for the escape of pus. A culture of the fluid should be made immediately so that the type of organism may be determined. The most treacherous of all the infecting organisms is the pneumococcus, type III. With this type of organism, the middle ear and drum may gradually clear up while the infection actually is progressing and burrowing deeper into the mastoid. Such a case should be watched very carefully. The different strains of streptococci will vary in their virulence from year to year and in different localities.

Chemotherapy has done a great deal to help control ear infections and their complications. By taking a culture early, the physician will know the type of infecting organism, and therefore will be able to select the proper chemotherapeutic agent to be used. If large doses of the drug are administered, the patient should be hospitalized, and the blood level of the drug and the blood count should be watched carefully. These drugs often mask symptoms which otherwise would serve to indicate the progress of the infection. Therefore, such a patient should be watched more carefully than one who is not receiving any of these drugs.

After the myringotomy the ear should be cleaned and inspected every day, especially if there is any fever. The dry method of treating acute ears, which is merely gently drying out the canal by sopping up the pus with cotton on the end of a probe, is to be preferred. Gentle irrigations of the canal may be given if the secretions are too thick to drain out properly, or if it is impossible for the physician to see the patient often enough to keep the ear clean. The nose should be treated until the ear is dry. The use of Haskin's suction is of great help in treating children who are too young to keep the nasal passages clean by blowing. Suction is delivered through a small soft rubber catheter, the end of which has been cut off and the sharp edges of the rubber softened and rounded by being passed through a flame. The catheter then is oiled and gently passed into each side of the nose back to the nasopharynx. One is often amazed at the amount of pus which can be aspirated.

The temperature and leukocyte count should be watched. If the perforation tends to become closed by the swelling of the surrounding tissues, 5 per cent phenol in glycerine may aid in keeping it open. It may be necessary to repeat the myringotomy. The presence of a profuse discharge may be very misleading. With increased pressure in the middle ear it is possible for a large amount of pus to escape through a very small opening. In such a case the ear may dry up rather rapidly after an ade-

quate opening is made. For this same reason a spontaneous rupture of the drum may give inadequate drainage. It is advisable to do a myringotomy on all cases which show a drum that is still bulging.

In most of the severe infections of the middle ear there is some inflammatory reaction in the mastoid, which may occur without any actual invasion of the infecting organism. There may be some mastoid tenderness in the first few days and a roentgenogram of the mastoid may show some clouding of the cells. If these symptoms do not persist after adequate drainage is established through the drum, and if the temperature does not remain unduly high, conservative treatment should be continued.

Once the infection breaks through the barriers at the additus, between the antrum and mastoid cells, and actually invades the mastoid, surgical intervention may be required. An increasing number of cases, however, are responding to the conservative treatments already outlined when they are combined with some form of chemotherapy.

The invasion of the mastoid usually is proclaimed by a further elevation of the temperature and leukocyte counts or a re-elevation, if they had returned to normal after the initial infection of the middle ear. There is pain in the ear and mastoid, and edema and tenderness over the mastoid. There is often a sagging of the posterior superior canal wall, which is manifested by a narrowing of the canal lumen from above and behind. A general toxic reaction occurs which in infants may take the form of severe prostration, diarrhea, dehydration, rapid loss of weight, and a high fever.

Where the infection becomes serious and the patient obviously is losing ground rapidly, surgical intervention may be necessary without delay; however, in most cases, it is best to delay operating upon the mastoid for a few days to allow some local resistance to the infection to develop. If operated upon too soon, new avenues for the absorption of toxins are opened and a severe septicemia and stormy convalescence may ensue. The advent of sulfanilamide and its allied compounds has greatly influenced this phase of the problem. It will frequently convert a surgical mastoid into a non-surgical one. Those that have to be operated upon do better if the patient is given chemotherapy for two or three days before the operation.

In cases in which delay is possible, the temperature usually subsides to a certain extent in a few days. If the indications for interference still are present, the operation should be performed. The roentgenogram may not always show breaking down of the intracellular septa, but when it does, operation should be performed immediately.

When the patient is recovering from his mastoid infection, usually on the tenth day of convalescence, the tonsils and adenoids should be removed, if present. Any sinus infection also should be corrected in order

to hasten convalescence and to prevent a recurrence of ear infection. If these procedures are delayed until the mastoid wound is practically healed, it is best to wait two or three months, because at this stage, the removal of the tonsils and adenoids may stir up the ear infection at a time when there will be no adequate drainage, and may necessitate reoperation.

The management of a mastoid infection is very difficult. One very dangerous situation is found in the cellular mastoid with a very thick cortex, which imprisons the infection in the deep cells of the mastoid. It may prevent tenderness or edema over the mastoid even when a very severe infection is progressing beneath it. A feeling of false security may be attained by the absence of tenderness over the mastoid and dire consequences may result. A brief outline of one case will serve to illustrate this situation.

A young physician developed an otitis media about five weeks before Christmas. He immediately consulted an otologist who performed a myringotomy. The following day the other ear was involved and also was opened. The ears continued to run for the ensuing five weeks and there was some elevation of temperature, but no tenderness over the mastoid. Because of this lack of tenderness, roentgenograms of the mastoid were not taken. He then drove two hundred miles to his home. Several days later there was a sudden elevation of temperature, headache, nausea, and vomiting. Still there was no tenderness over the mastoid. At first, intestinal influenza was suspected but when he failed to improve after a few days he was seen by a neurologist who immediately sent him to the hospital. Upon arrival he was found to have a well-developed meningitis with streptococci in the spinal fluid. Roentgen examination showed badly infected mastoids, with some breaking down of the cells, and an extremely thick cortex.This was verified at operation when both mastoids were completely cleaned out. However, it was too late to save his life and he subsequently died. This occurred before the development of sulfanilamide. His physicians were all led astray by the absence of tenderness over the mastoid.

If the acute condition subsides in any of the stages already outlined, the mechanism of the ear may return to a normal or nearly normal condition. There may be complete healing even after a mastoid infection. If there has not been great destruction of tissue, the function may return to normal. The perforation of the drum may heal and the scar may be pushed off to the periphery of the drum so that later inspection may show a perfectly normal appearing drum. This is especially true if a myringotomy has been done.

If the healing is not complete, a chronic condition ensues, such as tubal catarrh, in which deafness of the middle ear persists. Contrary to the textbook teachings, some of these cases may show a greater loss for the

higher tones than for the lower tones, giving the picture usually attributed to a nerve deafness. The drum is retracted and may show no other evidence of pathology. When the acute infection has completely subsided, the eustachian tube should be inflated. These cases also should have nasal treatments with tampons soaked in ephedrine solutions and the application of a fresh solution of 20 per cent argyrol to the eustachian openings in the nasopharynx. This usually will give relief.

If the hyperplasia of the mucous membrane extends into the middle ear cavity, a hyperplastic otitis media results. This usually is due to repeated mild and acute attacks. The drum is thickened, retracted, and shows a loss of lustre. Here again the treatment is directed toward the eustachian tube in an attempt to restore its patency by inflations and nasal treatments. Foci, such as tonsils, should be removed and nasal obstruction from a badly deviated septum should be corrected to prevent a recurrence of further acute episodes which will lead to further loss of hearing. If there are bands of adhesions within the middle ear, some deafness will remain and no treatment has been found yet which will combat it successfully.

An acute suppurative otitis media and mastoiditis may progress to a chronic otorrhea. This should not be allowed to continue for more than three or four months because the loss of hearing will be too great. In all chronic otorrheas there is some involvement of the mastoid cells, if any are present.

The patient with a chronic otorrhea should be examined carefully. First the adequacy of the perforation should be determined. It often is too small, or is located too high off the floor to give sufficient drainage. In such a case a myringotomy should be done. Sometimes a polyp will be found which protrudes through the perforation and fills the canal. This blocks the drainage and should be removed. These simple procedures may change the entire course of the infection.

The nose and throat should be examined for any possible foci which may contribute to the infection. Very often the removal of the tonsils and adenoids will result in healing of the ear condition. Any infection present in the sinuses should be adequately treated, and surgery performed if necessary. If the otorrhea still persists, further treatment depends upon the type of mastoid which is present, whether there is a cellular infected mastoid or a sclerotic noncellular one. The roentgenogram alone will differentiate the two types. If the mastoid contains infected cells, a mastoidectomy should be done. This type of chronic otorrhea, which is one of the most dangerous of all, and those with cholesteatoma are the ones which most often develop intracranial complications with acute exacerbations. As long as such a patient has otorrhea, the chances of serious complications are very great.

If the mastoid is sclerotic and noncellular the ear can be treated conservatively. One per cent thymol in seventy per cent ethyl alcohol is perhaps the most effective drug. This is instilled into the ear after it has been dried out carefully. Care should be taken to get the solution through the perforation and into the tympanum. A gentle negative pressure in the external canal will usually draw the air out of the tympanum and allow the fluid to enter. This can be done daily. Thymol iodide powder also is very useful and can be used later when the drainage decreases.

If the otorrhea persists and there are granulations or cholesteatoma in the middle ear cavity, and if the hearing is gone, a radical mastoid operation should be done. The radical operation does not always produce a dry ear but, by converting the mastoid and middle ear into one large cavity connected with the external canal, the danger of subsequent serious complications is removed.

# THE DIAGNOSTIC SIGNIFICANCE OF AN INCREASED Q-T INTERVAL IN THE ELECTROCARDIOGRAM

CHARLES P. WOFFORD, M.D. and A. CARLTON ERNSTENE, M.D.

The principal factor which influences the duration of electrical systole as indicated by the Q-T interval of the electrocardiogram is the heart rate.[1] In studies of the effect of other factors upon the length of electrical systole, corrections, therefore, must be made for the influence of variations in the heart rate. This can be done either by the use of the chart constructed by White and Mudd[1] or by employing Bazett's[2] formula: systole $= K\sqrt{\text{cycle}}$. For purposes of clinical application the use of the chart of White and Mudd appears to be more practical than the use of the formula.

Prolongation of the period of electrical systole often is observed in association with such electrocardiographic abnormalities as bundle branch block, ventricular paroxysmal tachycardia, ventricular premature beats and auricular paroxysmal tachycardia.[1] It also has been known for many years that a low serum calcium value may be accompanied by a prolonged Q-T interval,[1,3,4,5] and more recently[6] attention has been directed to the fact that a reduction in the concentration of the serum potassium may be responsible for lengthening of electrical systole. In two patients who had tetany, White and Mudd[1] observed a prolongation of the Q-T interval beyond the normal when the serum calcium content was extremely low (4 to 6 mg. per 100 cc.). When the serum calcium value rose above 6 mg. per 100 cc., however, the duration of the Q-T interval usually fell within the limits of normal. It would seem, therefore, that although a reduction in the concentration of serum calcium may fail to reflect itself in significant changes in the duration of electrical systole, the presence of a prolonged Q-T interval in an electrocardiogram showing none of the disturbances of conduction or rhythm mentioned above should suggest the possibility of a reduced concentration of serum calcium or serum potassium. The results of the present study confirm this opinion.

## MATERIAL AND RESULTS

Electrocardiograms and measurements of the concentration of serum calcium and phosphorus were made in fifteen patients (Table 1). Twelve individuals were suffering from acute or chronic parathyroid tetany but in none were the symptoms of more than moderate severity. The lowest serum calcium content recorded was 6.4 mg. per 100 cc. Two patients had hypocalcemia due to chronic glomerulonephritis; the lowest serum calcium value in one of these was 6.1 mg. per 100 cc. and in

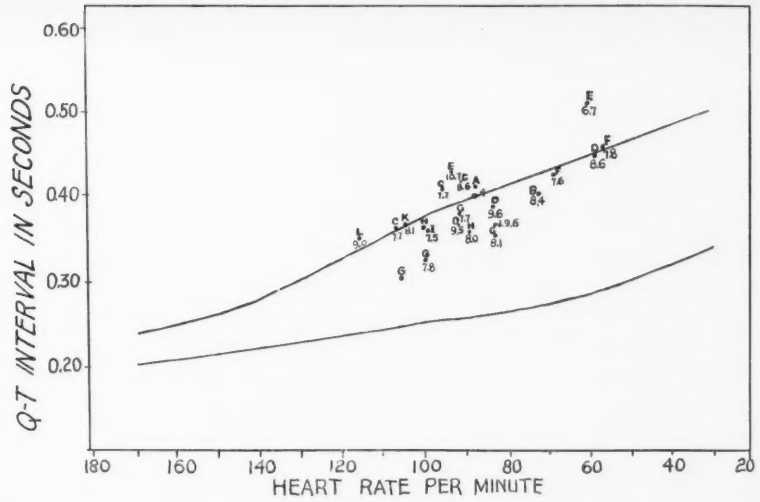


FIGURE 1: The Q-T Interval of Twelve Patients with Hypocalcemia Due to Postoperative Tetany.

The lines indicating the limits of normal for the Q-T interval are from the chart of White and Mudd[1]. The serum calcium content (in milligrams per 100 cc.) is indicated by the figure below each dot representing a Q-T interval.

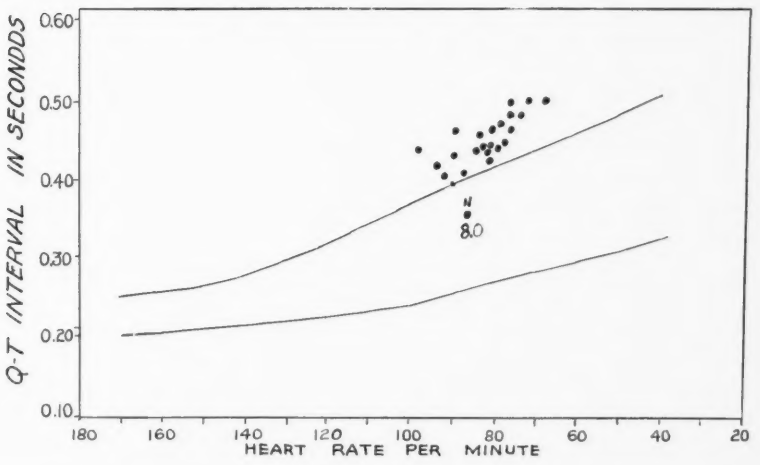


FIGURE 2: The Q-T Interval of Two Patients with Hypocalcemia Due to Chronic Glomerulonephritis.

The lines indicating the limits of normal for the Q-T interval are from the chart of White and Mudd[1]. The measurement on patient N is indicated by the letter above the dot and the serum calcium content by the figure below the dot.

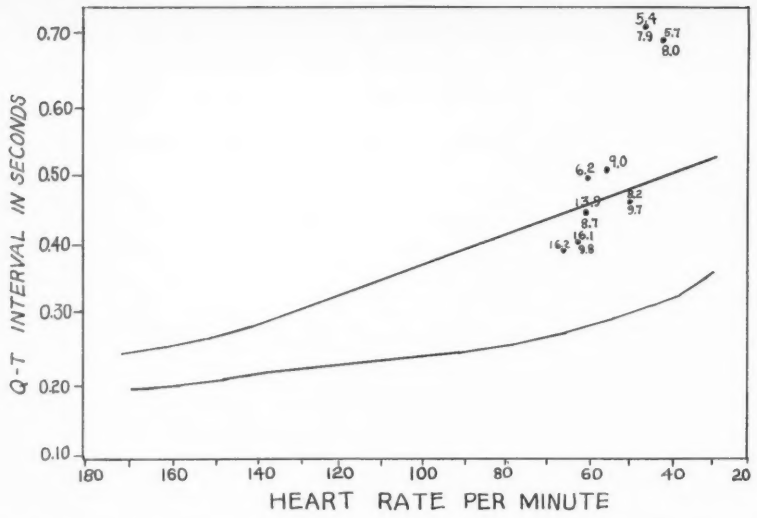


FIGURE 3: The Q-T Interval in a Patient with Addison's Disease Under Treatment with Desoxycorticosterone Acetate.

The lines indicating the limits of normal for the Q-T interval are from the chart of White and Mudd[1]. The serum calcium content is indicated by the figures below each dot representing a Q-T interval and the serum potassium content by the figures above the dot.

the other, 7.9 mg. per 100 cc. One person had Addison's disease and was being treated with desoxycorticosterone acetate. In this case the serum calcium concentration ranged from 7.9 mg. to 9.8 mg. per 100 cc.

The observations on the Q-T interval in the patients who had tetany are presented in Figure 1. In five of the twelve individuals the Q-T interval was found to be prolonged beyond the limits of normal on one or more occasions. Values at the upper limit of normal were recorded in two of the remaining patients, while in all of the others the duration always was perfectly normal. No suggestion of a mathematical relationship between the level of the serum calcium and the duration of the Q-T interval was observed.

In one patient with chronic glomerulonephritis and hypocalcemia, the Q-T interval was invariably prolonged (22 observations), while in the second individual the Q-T interval was normal in the one electrocardiogram which was made (Fig. 2).

The greatest prolongation of the Q-T interval was observed in the patient who had Addison's disease and who was being treated with desoxycorticosterone acetate (Fig. 3). The serum calcium concentration was higher in this individual than in many of the other patients studied. The serum potassium content, however, was greatly reduced

## TABLE 1

## THE DURATION OF ELECTRICAL SYSTOLE IN HYPOCALCEMIA

| *Case* | *Sex* | *Age* | *Date* | *Q-T Interval* | *Heart Rate* | *Serum Ca.* | *Serum P.* | *Remarks* |
|---|---|---|---|---|---|---|---|---|
| A | F | 39 | 8/12/39 | .40 | 87 | 6.4 | 4.4 | Resection of recurrent thyroid adenoma 8/10/39. Mild tetany. |
| B | F | 56 | 9/15/39 | .40 | 72 | 8.4 | 4.8 | Chronic postoperative tetany. Thyroidectomy, 1929. |
| C | F | 29 | 9/12/39<br>9/15/39 | .36<br>.41 | 107<br>93 | 7.7<br>7.7 | 4.2<br>5.5 | Thyroidectomy 9/9/39. Mild tetany. |
| D | F | 55 | 1/17/36<br>1/20/37<br>2/17/40 | .38<br>.36<br>.46 | 80<br>90<br>58 | 9.6<br>9.5<br>8.6 | 5.9<br>5.7<br>4.4 | Chronic postoperative tetany. Thyroidectomy, 1928. |
| E | F | 42 | 4/17/40<br>4/20/40 | .52<br>.40 | 60<br>92 | 6.7<br>10.7 | 5.9<br>2.6 | Chronic postoperative tetany. Thyroidectomy 7/14/39. |
| F | F | 51 | 5/13/40<br>5/14/40<br>5/16/40 | .41<br>.43<br>.47 | 83<br>66<br>57 | <br>7.6<br>7.8 | <br>6.4<br>5.3 | Resection of recurrent adenoma 5/10/40. Mild tetany. |
| G | F | 58 | 5/16/40<br>5/22/40<br>5/24/40<br>5/27/40<br>5/31/40 | .30<br>.42<br>.36<br>.36<br>.32 | 108<br>90<br>80<br>90<br>100 | <br>8.6<br>8.1<br>7.7<br>7.8 | <br>3.4<br>4.3<br>5.7<br>3.6 | Thyroidectomy 5/20/40. Mild tetany. Parathormone (100 units) daily from 5/27 to 5/30 and 30 gm. Ca. lactate orally. |
| H | F | 49 | 7/25/39<br>7/28/39 | .36<br>.36 | 100<br>88 | <br>8.0 | | Thyroidectomy 7/22/39. Moderately severe tetany. |
| I | F | 26 | 7/29/39 | .36 | 100 | 7.5 | 5.0 | Thyroidectomy 4/24/39. Mild tetany. |
| J | F | 29 | 8/28/39 | .36 | 80 | 9.5 | 5.5 | Thyroidectomy 11/20/23. Chronic mild postoperative tetany. |
| K | F | 40 | 9/18/39 | .36 | 105 | 8.1 | 4.3 | Thyroidectomy 9/16/39. Mild tetany. |
| L | F | 40 | 3/27/40 | .34 | 116 | 9.0 | 4.0 | Thyroidectomy 3/25/40. Mild tetany. |
| M | M | 46 | 8/26/39<br>8/28/39<br>8/29/39<br>8/30/39<br>8/31/39<br>9/1/39<br>9/5/39<br>9/6/39<br>9/9/39<br>9/11/39<br>9/12/39<br>9/15/39<br>9/16/39<br>9/18/39<br>9/19/39<br>9/20/39<br>9/22/39<br>9/23/39<br>9/25/39<br>9/26/39<br>9/28/39<br>10/18/39 | .50<br>.46<br>.44<br>.48<br>.44<br>.46<br>.50<br>.48<br>.50<br>.46<br>.44<br>.40<br>.40<br>.41<br>.45<br>.46<br>.44<br>.42<br>.42<br>.42<br>.42<br>.41 | 72<br>80<br>78<br>76<br>98<br>76<br>68<br>74<br>77<br>78<br>78<br>87<br>92<br>93<br>84<br>89<br>83<br>90<br>83<br>82<br>82<br>80 | 6.2<br>6.1<br><br>7.6<br>5.4<br>6.4<br>6.2<br>5.9<br>6.3<br>7.5<br>6.7<br>8.0<br>8.4<br>8.9<br>8.7<br>9.3<br>8.9<br>8.8<br>8.5<br>8.3<br>8.0<br>6.9 | <br>8.3<br><br>10.6<br>10.0<br>11.4<br>11.0<br>11.0<br>9.1<br>9.8<br>10.0<br>11.8<br>11.8<br>11.3<br>10.0<br>11.2<br>11.8<br>11.3<br>11.3<br>11.3<br>11.3<br>10.1 | Chronic glomerulonephritis. Given A.T. 10 from 9/1/39 to 9/22/39. Blood urea 162-243 mg. per 100 cc. Died 10/28/39. |
| N | M | 38 | 10/2/39<br>10/4/39<br>10/5/39 | <br>.34 | <br>86 | 8.0<br><br>7.9 | 9.1<br><br>10.4 | Chronic glomerulonephritis. Blood urea 330 mg. per 100 cc. |
| O | F | 37 | 3/2/40<br>3/11/40<br>3/20/40<br>4/5/40<br>4/17/40<br>4/25/40<br>5/2/40<br>11/2/40 | .68<br>.48<br>.50<br>.70<br>.46<br>.44<br>.40<br>.38 | 48<br>62<br>56<br>54<br>52<br>62<br>64<br>66 | 8.0<br><br>9.0<br>7.9<br>9.7<br>8.7<br>9.8 | 2.5<br><br>2.6<br>2.9 | Addison's disease, receiving desoxycorticosterone acetate. |

below normal during the earlier observations and later returned to normal. With this change the duration of the Q-T interval likewise became normal. Although the lowest serum calcium values were obtained when the Q-T interval was longest, the subnormal serum potassium concentration appeared to be of greater importance than the hypocalcemia in prolonging the Q-T interval.

## Summary and Conclusions

Electrocardiograms and measurements of the serum calcium concentration were made in twelve patients who had acute or chronic parathyroid tetany, in two individuals with hypocalcemia due to chronic glomerulonephritis, and in one patient with Addison's disease who was being treated with desoxycorticosterone acetate. The Q-T interval of the electrocardiogram was abnormally prolonged on one or more occasions in five of the twelve individuals with tetany, in the patient with Addison's disease, and in one of the two individuals with chronic glomerulonephritis. There was no apparent mathematical relationship between the level of the serum calcium and the duration of the Q-T interval. The greatest prolongation of the Q-T interval was observed in the patient who had Addison's disease and who was being treated with desoxycorticosterone acetate. In this patient the subnormal serum potassium concentration appeared to be of greater importance than the hypocalcemia in prolonging the Q-T interval.

The observations indicate that although hypocalcemia does not always increase the duration of electrical systole, the presence of a prolonged Q-T interval should lead one to consider the possibility of a subnormal concentration of either calcium or potassium in the blood serum.

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# PROCTOSCOPIC OBSERVATIONS IN GASTRO-INTESTINAL ALLERGY

*Report of Two Cases*

J. WARRICK THOMAS, M.D. AND R. JOHN F. RENSHAW, M.D.

## INTRODUCTION

Recent discussions concerning gastro-intestinal allergy prompted us to investigate methods whereby we might make direct observations of the character of the reaction produced when an allergen comes in contact with the mucosa of the gastro-intestinal tract. We were concerned not only with the local area involved but also with the symptom-complex resulting from such a reaction; namely, abdominal cramps, diarrhea, constipation, nausea and vomiting, pyrosis, etc. Four clinical methods of approach to this investigation were roentgenographic, gastroscopic, endoscopic through a fistula or in colostomy, and proctoscopic. The two case reports are concerned with the proctoscopic approach.

The two cases cited present findings typical of the proctoscopic approach to sensitization study. The technic entailed tap water enemas the night prior to examination. On the morning of examination, the proctoscope was introduced with a minimal amount of a non-irritating water soluble lubricant. The character of the rectal mucosa was noted and the rectal valves were identified as test sites. The allergens were applied in powdered form, using that amount which would adhere to the end of the cotton applicator. The tests were read in from five to twenty minutes, depending upon the rapidity of the reaction, and were graded from 1+ to 4+, according to the amount of erythema, edema, engorgement of the vessels, and hemorrhage present. Any symptoms resulting from the test such as cramps or lower abdominal distress were recorded.

## CASE REPORTS

*Case 1:* A thirty-five year old white woman who was first observed in July, 1939, complained of recurrent colds, bronchial asthma, recurrent urticaria, nasal obstruction, and frequent attacks of indigestion. She was subject to repeated head colds which were followed by asthmatic attacks on the average of once a month. She incriminated chocolate, onions, and certain other foods as causing her abdominal distress. Her gastro-intestinal symptoms were characterized by a "stomach full of gas and abdominal cramps." The family history of allergy revealed that a brother had hay fever.

Upon physical examination, the only significant findings of clinical value were scattered musical rales throughout both lung areas. Routine laboratory studies were non-contributory.

Endermal tests revealed positive reactions to many inhalants, molds, and bacteria, and definitely positive reactions to certain foods. However, the patient failed to react to onion or chocolate.

Chocolate and onion were selected for proctoscopic sensitization study because they had been incriminated by the patient, and had not reacted significantly by skin testing.

The allergens were applied to the rectal valve (in the manner outlined above) and five minutes later the patient complained of a "stomach full of gas and cramps." At this time the test sites were observed; there was no reaction to onion but a frank erythema in the area of the test with chocolate extract. The patient continued to complain of distress. The tests were checked at the end of fifteen minutes. The chocolate site revealed frank erythema, with some associated edema, and was classified as a 2+ reaction.

Her symptoms persisted for from two to three hours and required several enemas for relief. A program of management was outlined which included the elimination of chocolate from her diet.

*Case 2:* A twenty-nine year old white woman was first observed on February 5, 1939. She complained of persistent colds with associated cough for two months and generalized weakness and fatigue for six months. She described her condition as "run-down with no appetite and indigestion for the past six months." Her constipation over a period of two years was sufficient to require daily laxatives or enemas.

During the summer of 1938, she had experienced diarrhea with associated mucus, and bright bloody and watery stools. At that time she was told by a proctologist that she had "cryptitis and internal hemorrhoids." A hemorrhoidectomy was performed but did not control her rectal distress. The patient continued to have symptoms of gas and bowel distress varying with her diet, and she found it necessary to use frequent enemas in order to obtain relief.

Her nasal symptoms started in December, 1938, with a head cold, a non-productive cough, sore throat, and a daily elevation of temperature reaching 99.6° F. over a period of several weeks. She also reported a loss of thirty-one pounds during the previous six months. The patient stated that twelve months ago, she had had a bilateral otitis media with a mild chronic discharge over a period of months. Four weeks prior to her coming to the Clinic, she had an attack of influenza with high fever, associated with a "cloudy right maxillary sinus."

Her abdominal distress during the six months prior to observation was characterized by epigastric pain and fullness, coming on usually an hour after meals. Her symptoms were aggravated by cabbage and fried foods, and were relieved by baking soda. Occasionally she experienced nausea, but no vomiting.

During the past year she had had recurrent right sided headaches which were not associated with her menstrual period, and with no accompanying nausea or vomiting.

She gave a history of urticaria and tightness in the chest associated with wheezing. The family history was strongly positive for manifestations of allergy and, in addition, the patient had three children with perennial allergic rhinitis.

The physical examination revealed the nasal mucosa to be somewhat edematous and pale gray in character. The rest of the examination was essentially negative.

Proctoscopic examination revealed a dark brown, somewhat granular mucosa which was characteristic of the habitual use of cascara cathartics. The sigmoid colon was very spastic, and there was no evidence of ulceration.

The laboratory studies showed a blood eosinophilia of 4 per cent; 50° free acid and 70° total acid from the Ewald test meal; a negative undulant fever agglutination; and negative stool examination. Roentgen examination of the chest was normal. A gastro-intestinal roentgenogram revealed a normal stomach, duodenum and gall bladder, but a somewhat spastic colon with marked hypermotility. A retrograde pyelogram was negative.

The patient had a complete allergy survey and showed significant reactions to a number of foods, inhalants, and bacteria. She was placed upon a simple diet such as is used in a program of bowel management and, in addition, was instructed to eliminate not only the foods she suspected, but also those to which she had given strongly positive reactions. A program of hyposensitization and avoidance was instituted over a period of months.

When the patient was observed two months later, she reported that she had appreciated a definite improvement in her gastro-intestinal symptoms since following the combined program of bowel management and allergy restrictions. Three months later, she reported that she had only slight abdominal distress and had shown a definite gain in weight. She had found that beef, spinach, and lettuce caused definite discomfort, and she also suspected eggs, asparagus, beets, and apples.

At this time, skin and proctoscopic sensitization studies were made after the rectal mucosa had been observed and found to be normal. The findings were as follows:

| | *Skin Test* | *Proctoscopic Test* |
|---|---|---|
| Beef | negative | 2+ localized erythema, and edema |
| Eggs | ± | 4+ localized erythema, edema and several ruptured vessels |
| Lettuce | negative | questionable reaction |
| Asparagus | + | + |

Following the proctoscopic tests, the patient had slight abdominal and rectal distress with a feeling of spasm, and later developed severe cramps which lasted three to five hours. She required several enemas for relief. The incriminated foods were eliminated from her diet in conjunction with a program of restriction and allergy management.

The third observation was in February, 1940, at which time the proctoscopic tests were repeated. The mucosa was found to be normal and the following observations were made:

| | *Skin Test* | *Proctoscopic Test* |
|---|---|---|
| Beef | Not done | negative |
| Eggs | " | 2+ erythema and edema |
| Lettuce | " | 2+ erythema and edema |
| Asparagus | " | negative |

Following this test, the patient developed some mild lower abdominal cramps which lasted for from five to fifteen minutes. At this time, she reported that following the ingestion of a pudding containing egg, and also a lettuce salad, she had developed severe cramps which had necessitated the application of heat for relief. For a period of seven to eight months, the patient was relatively free of symptoms as long as she followed the program of management based upon the sensitization studies.

## Discussion

The two cited cases illustrate the type of reactions which are experienced and observed in gastro-intestinal allergy when certain allergens are applied to the rectal mucosa. The local reactions were characterized by erythema, edema, and vascular engorgement which preceded the patient's abdominal distress.

# REPORT OF A CASE OF HYPERTHYROIDISM

*which was associated with obesity, arteriosclerotic and hyperthyroid heart disease, severe diabetes mellitus, a febrile response to iodine, and possible undulant fever, and in which the diabetes was completely controlled without insulin following thyroidectomy.*

E. J. RYAN, M.D.

A sixty-one year old white woman presented herself at the Clinic in July, 1939, complaining of "heart trouble." For the preceding eight or nine years she had had attacks of rather rapid and irregular heart action, the patient herself being conscious of the irregularity. At first these had occurred at rare intervals of once or twice a year, but as time passed, they were noted with increasing frequency. During the preceding year she had had four or five such episodes, the most recent of which had lasted for six weeks. Effort dyspnea, orthopnea, vertigo and tinnitus were denied. Slight swelling of the left ankle had been noted for only a few days. Moderate pain in the left side of the chest was considered to be muscular in origin.

Enlargement of the anterior neck had been present for four or five years, and nervous tension had gradually increased during the preceding year. Obesity had been present for a long period of time and there had been no recent weight loss. Appetite alteration, hyperhidrosis and heat intolerance were denied.

In the light of subsequent developments, it is also interesting to note that no history of glycosuria, polydipsia, polyuria or fever was elicited.

The patient was restless, apprehensive and uncooperative. The height was sixty-four inches and the weight on admission was 237 pounds. The temperature was 98.2° F. The thyroid gland was moderately enlarged and nodular. A fine tremor was present. The right breast had been removed thirty years previously. Auricular fibrillation was present with an apical heart rate of 168 beats per minute and a radial pulse rate of 128. The left border of cardiac dullness was 12 cm. to the left of the midsternal line. A systolic murmur was audible at the pulmonic area. The blood pressure was 174 systolic and 88 diastolic. There was definite peripheral vascular thickening. Slight pretibial edema was noted. The lungs were clear and the abdominal examination was negative.

Urinalyses and blood counts were normal. The serologic reactions of the blood were negative. The blood sugar four hours postprandial was 142 mg. per 100 cc. The basal metabolic rate was plus 18 per cent. A roentgenogram of the chest revealed cardiac enlargement with fibrous infiltration at the hilum of each lung, and extension into the peripheral zone. An electrocardiogram confirmed the auricular fibrillation noted clinically, and an occasional ventricular premature contraction was present.

The patient was seen initially in the Department of Cardiology, where diagnoses were made of (1) nodular goiter with hyperthyroidism, (2) hyperthyroid-arteriosclerotic heart disease, functional capacity class 2, with enlargement of the heart, auricular fibrillation, and early congestive heart failure, and (3) obesity. She was seen in consultation by a member of the Surgical Division, who concurred in the diagnosis of low-grade hyperthyroidism, but with the reservation that further studies should be carried out after rest and digitalization. Determination of the diabetic status was deferred temporarily.

She returned three weeks later after digitalization and rest. Subjectively there had been very little change. Auricular fibrillation still was present, but the apical rate had fallen to 134 and the radial rate to 84. The basal metabolic rate was plus 37 per cent, and the fasting blood cholesterol was 134 mg. per 100 cc. The administration of digitalis was maintained in dosages of one and one-half

grains of the dried leaf daily; fifteen minims of Lugol's solution three times a day were prescribed, but it is very doubtful that the patient followed this recommendation. In another three weeks, she was admitted to the hospital for thyroidectomy.

In the hospital the usual preoperative routine of sedation, rest, and fifteen minims of Lugol's solution three times a day were prescribed. The temperature was normal on admission, but gradually rose and reached 101.8° F. (Chart 1) on the fifth hospital day. At that time, she noted nausea, generalized aching, and coryza. The latter condition was considered causative at first, but when it subsided and the fever continued, an undulant fever skin test was done. This was strongly positive. The undulant fever agglutination was negative, and the opsonocytophagic index revealed no phagocytosis. A course of sulfanilamide therapy was carried out without benefit to the patient. The pulse rate increased in spite of therapy.

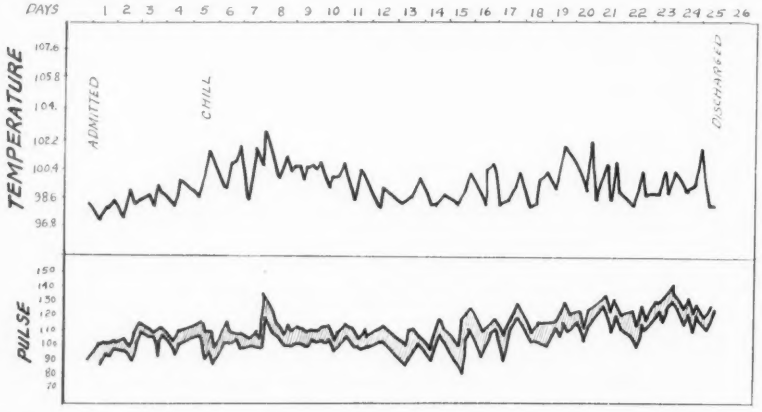


CHART 1: Temperature and pulse curves during hospital stay from August 22 to September 17, 1939.

Her diabetic progress during this period in the hospital is interesting. Because of the obesity, the diet was established and maintained at 1,140 calories daily. Initial blood sugars, fasting or four hours postprandial, ranged from 160 mg. per 100 cc. to 300 mg. per 100 cc. Standard (amorphous) insulin was started in small dosages and was rapidly increased to a total of 90 units in twenty-four hours. In spite of this, moderate hyperglycemia persisted, although glycosuria, which was never conspicuous, disappeared as a result of a relatively high renal threshold. Two days before dismissal, with a total twenty-four hour dosage of 85 units of protamine-zinc insulin and 20 units of standard insulin, blood sugars four hours postprandial ranged from 153 mg. per 100 cc. to 186 mg. per 100 cc. She was asked to continue a careful adherence to a weighed diet of the above caloric value, and to take 95 units of protamine-zinc insulin each morning.

Because the general condition of the patient afforded a contraindication to operation, and because of the possibility of undulant fever, the patient was dismissed on September 16, 1939, to continue therapy at home. Therapeutic recommendations included bed rest, maintenance doses of digitalis, five minims of Lugol's solution daily, and diet and insulin as outlined above. The adminis-

tration of roentgen therapy to the thyroid was to be considered at a later date. The prognosis was not considered good.

Within a few days after returning home, the temperature became normal and subjective improvement occurred. A course of undulant fever vaccine therapy was initiated soon thereafter by her local physician. Improvement in strength progressed and no symptoms of cardiac decompensation were observed. Auricular fibrillation continued. The diabetes remained under satisfactory control in spite of moderate excess over the prescribed diet, and the insulin dosages averaged 75 to 100 units of protamine-zinc daily. The weight fell gradually and in March was 166 pounds, representing a loss of seventy-one pounds in eight months.

The patient was not seen from September, 1939, to March, 1940, progress being reported by members of the family. On the latter date, when again studied, it was clear that the hyperthyroidism still was present, and thyroidectomy was advised. She entered the hospital for operation in June, 1940.

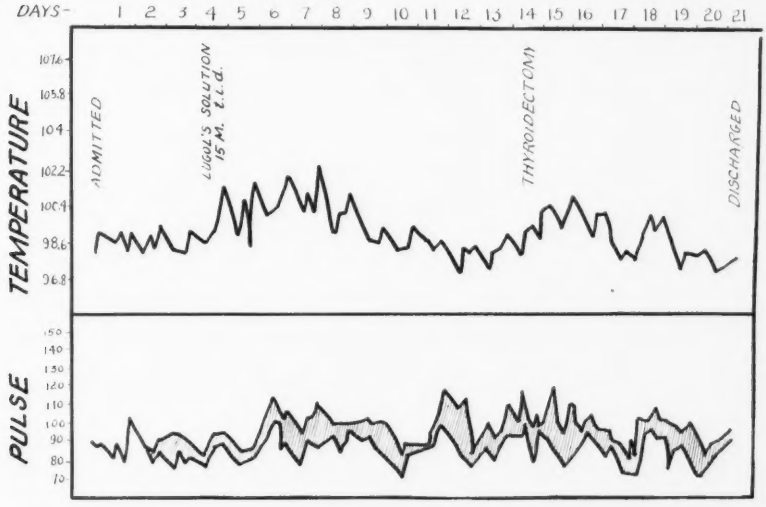


CHART 2: Temperature and pulse curves during hospital stay from June 4 to June 25, 1940.

For the first four days after admission the temperature remained normal. Lugol's solution then was given in dosages of fifteen minims three times a day. On the day after the administration of iodine was started, the temperature began to rise and fluctuated between 98.4° and 102.2° F. for five days (Chart 2). Lugol's solution was stopped on the fourth day of hyperpyrexia and large amounts of sodium chloride were given in an attempt to promote excretion of the iodine. The rise in temperature was considered to be the result of iodine medication. Subsequent small dosages of from five to ten minims of Lugol's solution once daily did not result in a recurrence of the elevation of the patient's temperature. The basal metabolic rate on the thirteenth hospital day was plus 24 per cent. Subtotal thyroidectomy was performed the following day. The convalescence was uneventful.

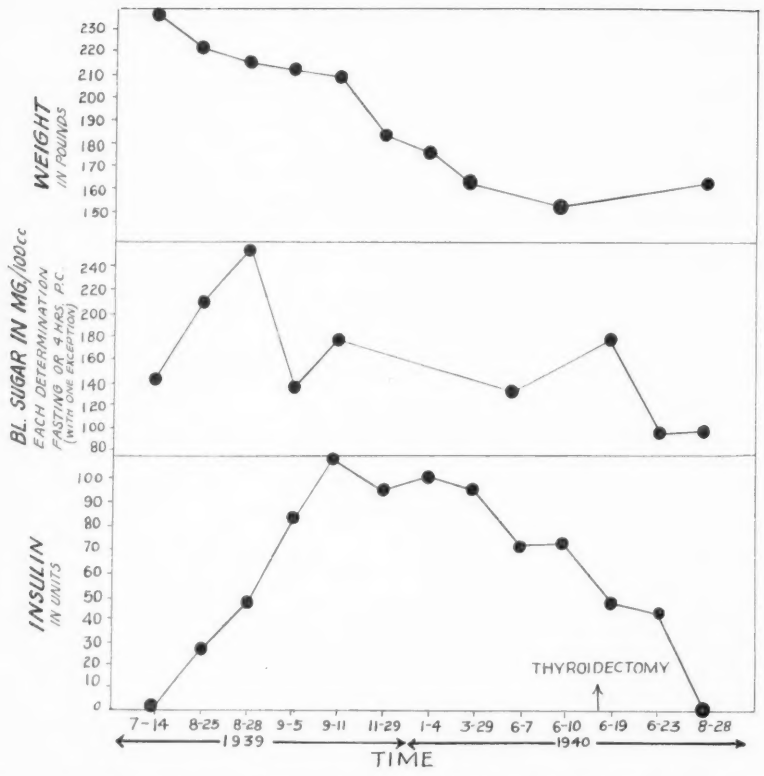


CHART 3: Representative readings showing weight, blood sugar, and insulin shifts from July, 1939, to August, 1940.

The patient continued to have auricular fibrillation during her stay in the hospital (Chart 2). Digitalis was maintained in dosages of one and one-half grains daily during the hospital stay, and after dismissal.

During the preoperative period the diabetes was well controlled on 75 units of protamine-zinc insulin daily, administered in one morning dose. Because of the more normal weight, the diet was increased first to 1,428 calories (carbohydrate content of 160 grams), and subsequently to 1,590 calories (carbohydrate content of 175 grams). Within a day or two postoperatively the insulin requirements fell to 50 units daily, and at the time of dismissal on June 25, 1940, had fallen further to only 40 units daily.

She returned two months later. The only outstanding complaint was of recurrent smothering attacks, which were considered to be of vagotonic origin. Auricular fibrillation was present with a ventricular rate of 80, but there was no evidence of cardiac failure. The basal metabolic rate was minus 12 per cent. The dose of insulin had been reduced gradually and it had been discontinued two weeks before the patient's reentry. Dietary recommendations had been followed moderately well. The fasting blood sugar was 100 mg. per 100 cc., and two and one-half hours after a meal containing 31 grams of carbohydrate, 13

grams of protein, and 14 grams of fat, it was 86 mg. per 100 cc. The weight had increased from 152 pounds a few days postoperatively to 161 pounds. Chart 3 represents in graphic form the weight shift, a few representative blood sugar determinations of the many done, and the insulin requirements. With one exception, all blood sugar determinations were made while fasting, or four hours postprandial.

Sedation was prescribed, digitalis administration was maintained, and she was asked to continue the same dietary program.

## Comments

*Dr. E. J. Ryan:* There are two factors in this case which could have contributed to a decrease in carbohydrate tolerance, and which justifiably raise the question of the presence of true diabetes mellitus. These are hyperthyroidism, and obesity of long standing. The absence of any significant degree of glycosuria likewise may be considered evidence against true diabetes. Because of the hyperthyroidism, hyperlipemia would not be expected and could not be considered of benefit in establishing the diagnosis. Degenerative changes, manifested particularly by rather marked peripheral arteriosclerosis and arteriosclerotic heart disease, favor a diagnosis of diabetes. However, there were no striking retinal changes. Glucose tolerance tests would have been helpful, but were not permitted by the patient.

Because of the relatively mild character of the hyperthyroidism, making the initial diagnosis difficult, and because of the relatively severe diabetes, probably hyperthyroidism occurred coincidentally with or was superimposed upon a true diabetes mellitus. If such were the case, the influence of hyperthyroidism upon the severity of diabetes, particularly as measured by insulin requirements, was strikingly demonstrated. The mechanism by which this action occurs is not understood clearly. Factors other than the thyroidectomy which probably contributed in some degree to the improved diabetic status are correction of the obesity, maintenance of reasonably good diabetic control, and the use of a diet of relatively high carbohydrate content.

Further observation of this patient from the diabetic standpoint is indicated, since it is not uncommon to observe a recurrence of hyperglycemia in such cases. This could be anticipated in this partiular instance should the patient become careless in her dietary regimen with resultant obesity, or should severe infection of any type develop.

At the time of the positive undulant fever skin test, it was felt that this disease was a contributing factor in her requirement for large quantities of insulin. In the light of subsequent developments, it is probable that the febrile course on that occasion was a result of iodine medication, just as it was shortly before operation.

The simultaneous occurrence of obesity and hyperthyroidism has not

been common in our experience. It is dependent, of course, upon a caloric intake which exceeds the individual's requirements, even when the metabolism is materially accelerated as a result of thyroid hyperactivity. Children with Grave's disease not uncommonly gain weight. Management of the obesity in this case differs in no significant respect from the program usually followed for correction of this condition.

*Dr. George Crile, Jr.:* This case is unusual because of the following features:

1. The patient's febrile response to the administration of iodine.

2. The rapid onset and severity of the diabetes and its complete control following thyroidectomy.

A febrile response to iodine rarely is seen in patients with hyperthyroidism. Barker and Wood[1] reported a group of seven cases which showed this reaction to iodine therapy, an incidence of 1.75 per cent in the 400 cases in their series. This is only the second case we have observed in which fever resulted from the administration of iodine, which disappeared following the withdrawal of the drug, and reappeared when iodine was given again. No explanation of this phenomenon has been made. It is important, however, to bear this reaction in mind when a patient with hyperthyroidism under treatment with iodine develops a fever. Small doses of iodine, such as 5 minims of Lugol's solution three times a day, usually are well tolerated, even when severe febrile reactions have been caused by the larger doses.

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# THE NEPHROTIC SYNDROME

*Report of Two Cases*

R. H. McDonald, M. D.

The outstanding clinical feature of the nephrotic syndrome is a generalized persistent type of edema, frequently of severe degree, associated with remarkably little subjective discomfort. Remissions without obvious cause are characteristic of the syndrome. Frequently, the patient is able to carry on his ordinary occupation without distress or discomfort over long periods of time. The patient's appearance often is strikingly suggestive of severe hypothyroidism, and it is interesting to note that both conditions have the common finding of lowered basal metabolic rates and increased blood cholesterol levels.

The nephrotic patient regularly shows a heavy proteinuria, this being due largely to the increased permeability of the glomerular capillaries to albumen, although all fractions of the protein of the blood plasma participate to some degree. Microscopic examination of the urine regularly reveals the presence of large numbers of granular, hyaline, and epithelial casts which are evidence of the severe tubular damage which is pathologically characteristic of the lesions. A few white blood cells commonly are present. In the majority of instances, red blood cells are lacking. Study of the urinary sediment with the polarizing microscope reveals the presence of doubly refractile lipoid bodies which are considered largely pathognomonic of the condition. However, their presence in the urine has been shown in other degenerative lesions of the tubular epithelium.

The most characteristic finding in the laboratory examination is a reduction in total plasma protein which may fall well below the level at which edema occurs. The protein loss is chiefly in the albumen fraction and is considered to be due to the smaller size of the albumin molecule which allows it to pass more readily through the capillary endothelium. Therefore, a reversal of the albumin-globulin ration commonly is seen. The hypoproteinemia results in lowering of the colloid osmotic pressure of the blood, and forms the basis for the severe edema.

Azotemia is not an ordinary feature in the nephrotic syndrome, and occurs only with complications or in terminal stages of the disease. In accordance with this finding the urea clearance test ordinarily shows only minor reductions in the renal reserve as far as the excretion of urea is concerned. Elevation of blood cholesterol to two or three times the normal level is a common finding and is associated with a lowered metabolic rate, even when the increased body weight due to retained fluids is taken into account.

The nephrotic syndrome is seen in any of the types of degenerative

Bright's disease, but more particularly in idiopathic degenerative Bright's disease, or lipoid or cryptic nephrosis. In degenerative Bright's disease associated with poisoning from heavy metals, toxemia of eclampsia, or associated with a generalized infection, the complete nephrotic picture rarely develops. In these cases the outlook is much better, as far as the renal lesion is concerned, than in the cases of genuine or lipoid nephrosis which, in our experience, have had a uniformly progressive downhill course often over a period of years. In a few instances also, the nephrotic syndrome has been seen in patients who undoubtedly had at the onset a primary hemorrhagic type of nephritis. After a few weeks or months some of these patients have developed the clinical picture which is not distinguishable by clinical and laboratory findings from the true lipoid nephrosis of idiopathic origin. However, a persistent microscopic hematuria may be found.

The etiology of the nephrotic syndrome still is obscure. Some have regarded it as being due to a general metabolic disease which causes some alteration in plasma proteins as a result of which they are more readily excreted, rather than to any specific renal lesion. The general conception, however, is that it constitutes a specific pathological renal entity of primary degenerative character. However, a few cases are found in which the nephrotic syndrome appears to be a sequel of ordinary hemorrhagic nephritis.

Treatment of the nephrotic syndrome is entirely symptomatic and, therefore, is applicable no matter what the origin has been. The marked proteinuria and plasma protein deficit logically suggests the desirability of a large protein intake which usually is well tolerated. Attempts also have been made to raise the plasma protein level directly by the use of transfusions of whole blood or blood plasma. Large and repeated transfusions are necessary to cause any appreciable increase in these levels and the results obtained are frequently disappointing because of the constant proteinuria. Some therapeutic success from the use of lyophile serum has been reported by Aldrich et al.[1] An attempt has been made to raise the osmotic pressure of the blood by the use of artificial substances such as acacia. Xanthine diuretics have proved useless. The use of potassium salts alone as a diuretic, and particularly in preparation for the injection of the mercurial diuretics, has been more successful. The oral administration of urea in quantities varying from 15 to 60 grams a day has given marked symptomatic improvements in several patients. However, care must be exercised when using this material in those patients who have suffered glomerular damage as indicated by low values for the urea clearance test. The lowered metabolic rate uniformly found in these patients has suggested the use of thyroid extract. It is well tolerated and large doses may be given with symptomatic benefit,

but little diuretic effect generally is obtained. The lowered metabolic rate probably is related to general undernutrition rather than to a specific thyroid deficiency.

## Case Reports

*Case 1:* A fifteen year old boy was first seen on January 3, 1940, with a complaint of generalized swelling which had been present for six months. It had developed insidiously without obvious cause, and had persisted steadily with minor fluctuations in degree. Apart from the swelling, the patient felt generally well. His previous history included attacks of what was considered to be scarlet fever in 1933 and in 1934. He had had tonsillitis frequently as a child and tonsillectomy had been performed in 1932. He had had measles, mumps, and chickenpox in childhood.

Examination showed him to be a well-developed, well-nourished boy, with generalized edema of the face, neck, trunk, and extremities. The temperature was 98° F., the pulse rate 100, and blood pressure, 120 systolic, 80 diastolic. Pupillary reactions were normal. The optic discs were outlined clearly and the retinae appeared normal. Dental examination showed the presence of Vincent's infection with marginal gingivitis. The tonsils had been removed cleanly. Two small cervical lymph glands were palpable. The thyroid was not enlarged. The chest was clear to percussion and auscultation. The heart was of moderate size, the rate regular and rhythmical. No abdominal masses were present. Neurological examination showed the reflexes to be normal.

Urinalysis consistently showed a heavy albuminuria with a high specific gravity. Microscopically a few white blood cells were noted regularly, but no red blood cells were seen at any time. A few coarsely granular and hyaline casts were found. Examination of the blood revealed 4,330,000 red cells, 7,350 white cells, and 78 per cent hemoglobin. The differential white count showed no abnormality other than the presence of a high percentage of fragile leukocytes. The fasting blood sugar was 98 mg. per 100 cc. The blood urea was 36 mg. per 100 cc. The total serum proteins were 3.5 mg. per 100 cc. of which the serum albumin constituted 1.6 mg. per 100 cc. and serum globulin 9 mg. per 100 cc. The total urinary protein on one occasion reached 9 mg. per 100 cc. Examination of the urine showed doubly refractile material but no anisotropic bodies. Wassermann and Kahn tests of the blood gave negative reactions. The basal metabolic rate was minus 35 per cent. An electrocardiogram revealed sinus tachycardia with a rate of 114 per minute. Blood cholesterol was 440 mg. per 100 cc.

The patient was given a high protein diet, repeated blood transfusions, and thyroid extract. He also was given a course of six injections of lyophile serum varying between 25 to 50 cc. after a preliminary intradermal test for sensitivity to the material had proved negative. Each injection of the lyophile serum was followed by a chill and febrile reaction which subsided within a short period of time. When discharged from the hospital on February 7, 1940, the edema almost had disappeared. However, the serum proteins were reported as 3 mg. per 100 cc.; the serum albumin, 1.6 mg. per 100 cc.; and serum globulin, 1.7 mg. per 100 cc.

*Case 2:* A girl, fifteen years of age, was admitted to the Cleveland Clinic on April 4, 1940, with a history of swelling about the face and eyes, and edema of the ankles which had been first noted in October, 1939. From that time until

the period of admission the patient had gained thirty-five pounds in weight. There had been occasional nausea and vomiting but no headaches. A low fever reaching as high as 100° F. had been experienced intermittently over a period of some months. At times there had been some elevation of blood pressure, but the exact levels were not known. Albumin with casts and occasional blood cells also had been found in the urine regularly. In January, 1940, the patient had a spontaneous remission of all her symptoms and a complete loss of edema. However, a month later the symptoms recurred. She had had an attack of influenza in February, 1939, and apparently had an upper respiratory infection in September of the same year. Recovery apparently had been normal. At the time of admission, the patient's only complaint was that of persistent swelling.

Physical examination showed a well-developed, over-nourished girl with marked generalized edema, particularly about the face. The temperature was 98° F., the pulse 88, and the blood pressure 120 systolic and 90 diastolic. The optic discs were clearly outlined and the retinae appeared normal. The tongue was moist. There was good oral hygiene, and the tonsillar fossae were clean. No lymph glands or thyroid enlargement were palpable. The chest was clear to auscultation and percussion. The heart was not appreciably enlarged and the rate was regular and rhythmical. There was no evidence of enlargement of the abdominal viscera or kidneys. Neurological examination showed the reflexes to be normal with no evidence of sensory or motor disturbance. Routine urinalysis revealed a pH of 6, four plus albumin, no sugar and a specific gravity of 1.038. Microscopically, numerous red and white cells with a few hyaline casts were seen. Blood counts revealed 4,720,000 red cells, 8,800 white cells, and 84 per cent hemoglobin. The total serum proteins were 5 mg. per 100 cc., serum albumin 2.2 mg. per 100 cc., and serum globulin 2.8 mg. per 100 cc. The fasting blood sugar was 77 mg. per 100 cc., blood urea 27 mg. per 100 cc., and blood cholesterol 820 mg. per 100 cc. The urea clearance test showed 50 per cent function the first hour, and 55 per cent the second hour. Wassermann and Kahn tests of the blood gave negative reactions.

The patient was placed upon a high protein, low sodium, high potassium diet. The use of ammonium chloride enteric coated tablets was started. During her hospital stay she received four injections of solyrgan, 0.5 to 1 cc. intravenously. Three transfusions of 500 cc. of blood were given. Urea was given as a diuretic by mouth, 20 gm. three times daily, but its use became inadvisable after a few days because of an increase in the blood urea level to 153 mg. per 100 cc. This urea retention subsided quickly when the material was withdrawn. Three injections of lyophile serum were given during the hospital stay. Each injection was followed by a marked febrile reaction, but without any remarkable diuretic effect. At the time of discharge from the hospital the total blood serum proteins were 4.6 mg. per 100 cc., serum albumin 2.2 mg., and serum globulin 2.4 mg. per 100 cc. The blood cholesterol, however, even though still above normal, had been reduced to 490 mg. per 100 cc.

## SUMMARY

The first case represents true degenerative Bright's disease or genuine nephrosis of unknown etiology with characteristic findings. The second case apparently had developed the clinical nephrotic picture in the course of or at least subsequent to a primary hemorrhagic nephritis. Both showed some improvement on intensive therapy but it is obvious that no radi-

cal improvement has occurred in the underlying renal lesion. In general, such lesions tend to progress gradually with eventual termination from renal failure or intercurrent infection.

The lyophile serum used in the treatment of these cases was supplied through the courtesy of Dr. Joseph Hughes, the Pennsylvania Hospital, Philadelphia, Pennsylvania.

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# STILBESTROL IN THE TREATMENT OF OVARIAN DEFICIENCY

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A female sex hormone which possesses the properties of the follicular hormone, and which is orally active, highly potent and cheap is of interest to most clinicians. Diethylstilbestrol (stilbestrol) is such a substance. It was first described by Dodds[1,2] and his co-workers. It is one of several related synthetic substances derived from a stilbene nucleus. Its formula is 4:4′-dihydroxy-a: β-diethylstilbene, bearing no relationship to the formula of any known natural estrogen.

Both experimentally and clinically it has been shown to possess many, if not all, of the properties of the natural estrogens. In addition to the form mentioned above, the dipropionate and the acetate have been used.

Stilbestrol in the several forms used clinically has been demonstrated to have the following properties:

1. The production of a follicular type of response in the genital tract of human beings and animals.
2. Inhibition of the excess production of gonadotropic hormone in castrates.[3]
3. Proliferation of the nipples and duct tissue of the breasts.[4]
4. Inhibition of lactation post-partum.[5]
5. Production of secondary sex characteristics in female hypogonadism.[4, 6]
6. Regulation of some cases of menstrual arrhythmias.
7. Relief of various subjective symptoms attributable to ovarian deficiency, such as menopausal symptoms, premenstrual headache and nervous tension, and certain associated states of mental depression and chronic exhaustion.
8. It relieves senile vulvovaginitis and cures gonorrheal vaginitis in children.[7]

Stilbestrol is effective by mouth, by intramuscular injection in oil, in suppositories, and by implantation subcutaneously as pellets.[8] The oral and intramuscular dosage has varied from as little as 0.1 mg. daily to as much as 60 mg. daily. However, doses in excess of 5 mg. daily have not been used often. When given in cases of menstrual arrhythmia, it may be used at times to best advantage in conjunction with progesterone. So-called toxic effects, chiefly nausea, have limited its use in some hands and have discouraged it in others.[3, 9]

## METHODS AND MATERIALS

We have administered the drug to over eighty patients. Forty of these whom we have been able to observe carefully have been selected as the

## TABLE 1

| Case No. | Stilbestrol Daily Dose Mg. | | Stilbestrol Relieved | | | | | | | | | | | | Stilbestrol Produced | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Initial | Maintenance | Previous Estrogen Treatment (Estradiol-B given by injection in every case) | Hot Flashes | Headaches | Depression | Irritability | Exhaustion | Psychoneurosis | Breast Pain | Joint Pain | Menorrhagia | Metrorrhagia | Hypomenorrhea | Pruritus | Nausea | Vomiting | Abdominal Distress | Headache | Remarks |
| 1 | 0.25 | 0.25 | Estradiol-B | | | | | | | Yes | | Yes | | | | | | | | |
| 2 | 1.0 | 1.0 | Estradiol-B | | | | | | | | | Yes | | | | | | | | |
| 3 | 0.25 | 0.25 | None | | | | Yes | | | | | Yes | | | | | | | | Given only with Estradiol |
| 4 | 0.5 | 1.00 | | | Yes | | | | | | | Yes | | | | Onset | | | | |
| 5* | 0.25 | 1.00 | Estradiol-B | | No | | | Yes | | | | | | | | | | | | |
| 6 | 0.5 | 0.5 | | | | | | Yes | | | | | | | | | | | | |
| 7 | 0.5 | 1.0 | Estradiol-B | | | | | | | | | | No | | | Yes | Yes | | | Not tolerated |
| 8 | 0.25 | 0.5 | | | | Yes | | Yes | | | | | | | | | | | | |
| 9 | 0.5 | 0.5 | Estradiol-B | | | | | Par. | | | | | No | | | | | | | |
| 10 | 0.25 | 1.5 | | | | | | | | | | | | | | | | | | Hemorrhagic cystitis |
| 11* | 1.0 | 2.0 | Estradiol-B | Yes | | Yes | | | | | | | | Par. | | | | Yes | | |
| 12 | 0.25 | 2.0 | | | Yes | | | | | | | | | Yes | | | | | | |
| 13 | 0.25 | | Estradiol-B | | Yes | | | | | | | | | | | Mild | | | | |
| 14 | 0.25 | 0.5 | | | Yes | | | | | | | | | | | | | | | |
| 15 | 0.25 | 0.5 | Estrone | Yes | | | | | | | | | | | | | | | | |
| 16 | 0.75 | 0.75 | Estrone | Yes | | Yes | | | Yes | | | | | | | | | | | |
| 17 | 0.25 | 1.0 | Estradiol-B | Yes | | Yes | | | | | | | | | | | | | | |
| 18 | 0.25 | 0.5 | Estradiol-B | Yes | | Par. | | | | | | | | | | | | | | |
| 19 | 0.25 | 0.5 | Estrone | Yes | | Yes | | | | | | | | | | | | | | |
| 20 | 0.25 | | | | | | | | | | | | | | | Severe | | | | Not tolerated |
| 21 | 0.1 | 1.5 | Estradiol-B | Yes | Yes | | | Yes | | | | | | | | | | | | |
| 22 | 0.1 | 0.5 | Estradiol-B | Yes | | | | | | | Yes | | | | | | | | | |
| 23 | 0.25 | 0.25 | | Yes | | | | | | | | | | | | Onset | | | | |
| 24 | 0.25 | 0.75 | | | | Yes | | | Yes | | | | | | | | | | | |
| 25 | 0.25 | | Estrone | Yes | | | | | | | | | | | | | | | | |
| 26 | 0.25 | 0.5 | | Yes | | Yes | Yes | Yes | | | | | | | | Mild | | | | |
| 27 | 0.25 | 0.5 | | ? | | | | | | | | | | | | Severe | | | | Not tolerated |
| 28 | 0.5 | | | | | | | | | | | | | | | | | | | |
| 29 | 0.25 | 1.0 | Estradiol-B | | Yes | | | | | | | | | | | | | | | |
| 30 | 0.25 | 1.5 | Estradiol-B | Yes | No | | | | | | | | | | | | | | | |
| 31 | 0.25 | 0.5 | | | Yes | Yes | Yes | | | | | | | | | | | | | |
| 32 | 0.25 | 0.25 | | | | | ? | | | | | | | | | | | | Yes | |
| 33 | 0.25 | 0.75 | Estrone | | Par. | Par. | | | | | | | | | | | | | | |
| 34 | 1.0 | 1.0 | | Yes | | | | | Yes | | | | | | | | | | | |
| 35* | 0.1 | 0.5 | | Yes | | Yes | | | | | | | | | | | | | | |
| 36 | 0.5 | | Estradiol-B | | | | | | | | | | | Yes | | | | | Yes | Not tolerated |
| 37* | 0.5 | 1.0 | | | | | | | | | | | | | Yes | | | | | |
| 38 | Oint ment | | | | | | | | | | | | | | | | | | | |
| 39 | 0.25 | 0.50 | Estradiol-B | | | Yes | Yes | | | | | | | | | | | | | |
| 40 | 0.25 | 0.25 | | | | Yes | | | | | | | | | | | | | | |

Estradiol-Benzoate was in the form of progynon-B, Schering Corp.
Estrone was in the form of Theelin, Parke Davis and Co.
* See text.

basis of this report (Table 1). They have been treated for periods of from one to thirteen months. There were twenty-four menopausal cases, fifteen cases of partial ovarian deficiency of various types, and one case of senile vulvovaginitis. The dosage of stilbestrol given varied from 0.1 mg. to 2 mg. daily. In most cases, the initial daily dose was 0.25 mg., and was increased gradually to 0.25 mg. several times daily, if necessary. Increase in the number rather than in the size of dosages was practiced in most cases. The estrogenic response was studied by means of vaginal smears.

In only two cases was stilbestrol administered intramuscularly; one patient received a single dose of 2 mg. of stilbestrol and was nauseated, weak, and stuporous for thirty-six hours; she subsequently took a therapeutically effective dose by mouth without discomfort (Case 30). The other patient took 0.1 mg. intramuscularly every other day with complete relief of symptoms but she could not maintain this relief constantly on twice that dosage by mouth.

## Menopause

These cases include seven of surgical menopause, thirteen with menopausal symptoms and amenorrhea for various periods, and five who had climacteric symptoms but who still were menstruating. The average dose of stilbestrol required for complete symptomatic relief was 0.6 mg. daily. The castrates required only a slightly higher dose than the others.

Seventeen patients complained of hot flashes. Fourteen were relieved completely, and one was not relieved, possibly because of severe hypertension which has been present in others in whom the hot flashes were difficult to ameliorate; two others did not tolerate the drug. Relief of depression and irritability accompanied relief from hot flashes. Headaches were present in four cases; one did not tolerate the drug, one had partial relief, and two had complete relief. Complaints such as exhaustion and irritability, attributable to the menopause, were relieved constantly. Joint pains were relieved by stilbestrol in one case and recurred on its withdrawal. One patient had complete relief of pain of right sciatic distribution both from estrone† and from stilbestrol.

## Hypo-Ovarianism

Of fifteen cases of ovarian insufficiency, three were unable to tolerate a therapeutic dose, one had stilbestrol only in conjunction with estradiol benzoate*, seven had marked relief or complete cessation of symptoms, and four showed improvement. Two of the latter probably had insufficient dosages; the other two were cases of anorexia nervosa. In these the

† Theelin, Parke Davis & Co.

* Progynon-B, Schering Corp.

estrogenic response, judged by vaginal smears, was good but the total clinical benefit was slight. The same result had been obtained with large doses of estradiol benzoate.

Symptoms other than disturbances in menstrual flow and rhythm included premenstrual headache and irritability, chronic exhaustion, hot flashes, and decrease in sexual libido. One case had increased libido. Premenstrual headaches were relieved completely in all of four cases, hot flashes were abolished, and other symptoms were affected to a variable extent. Judging by repeated volunteered statements, we have found that stilbestrol produces a feeling of energy and well-being usually equal to that produced by the natural estrogens.

Of the fifteen cases of hypo-ovarianism, seven had menstrual disturbances, not including a case of amenorrhea due to hysterectomy. Four of these exhibited menometrorrhagia, two had irregular scanty periods, and one had regular periods but a scant flow. Of the menometrorrhagias, Case 1 established a regular normal menstrual cycle with the use of 0.25 mg. of stilbestrol daily. Case 2 had a premenstrual endometrium which was of the early regenerative type, the equivalent of a normal endometrium of less than one week's development. Regular menses were established by the cyclic use of stilbestrol-progesterone, simulating the method used by Hamblen[10] and Ryan[11], in the treatment of menometrorrhagia with cyclic estrone-progesterone. The dose of stilbestrol in this case was 1 mg. daily for the first twenty-five days of the cycle, and 2 mg. of progesterone intramuscularly on the twenty-second, twenty-third, twenty-fifth, and twenty-sixth days of the cycle. Case 3 took stilbestrol in conjunction with cyclic estradiol-benzoate-progesterone therapy, and the part of stilbestrol in the successful result cannot be evaluated. Case 4 complained of profuse infrequent periods; following 1 mg. of stilbestrol daily they became more frequent and scant; insufficient dosage was indicated by subnormal vaginal smears and incomplete relief of symptoms. Cases 7 and 11 did not tolerate the drug. Case 12 complained of premenstrual headache and had a regular rhythm; on one occasion during treatment, a period was delayed. Thereafter the drug was regularly withdrawn for one week preceding the menses and the cycle continued regularly.

## Discussion

*Establishment and duration of effect:* The time required for the full therapeutic effect has been variable, due in part to the practice of beginning with small doses and gradually increasing them. Case 35 had marked relief of hot flashes within twenty-four hours after a single intramuscular injection of 0.1 mg. Other cases receiving gradually increasing daily doses have had gradual elimination of symptoms over periods of from one week to two months. Most patients experience sub-

FIGURE 1: Vaginal smear from surgical castrate, untreated. (X225)

jective benefit within three days after beginning stilbestrol therapy and obtain a maximum effect from a given dose within ten to fourteen days.

The time required for a relapse upon withdrawal of the drug has varied in most cases from four days to two weeks. A few have had no recurrence until weeks or months after withdrawal, and some have had

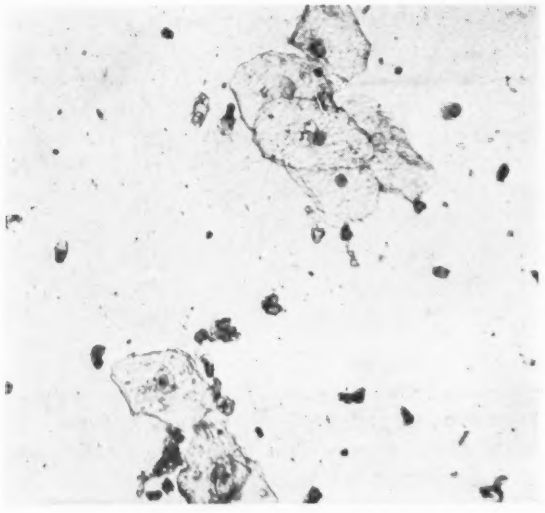

FIGURE 2: Vaginal smear showing partial estrus effect. (X225)

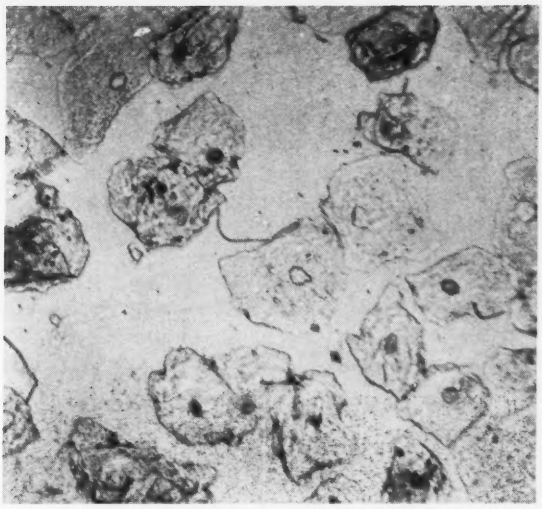

FIGURE 3: Vaginal smear showing full estrus effect. (X225)

no recurrence; obviously, this cannot be due to persistence of stilbestrol activity.

The vaginal smear changes are not so prompt as the symptomatic changes. Relief produced by stilbestrol in one or two days is not reflected in the smear until several days later. Evidence of withdrawal in the smear tends to be slower than the appearance of withdrawal symptoms by one or two weeks. This is similar to the experience of MacBryde et al.[12]

Vaginal bleeding upon withdrawal of the drug occurred in a few cases one to two weeks after stopping the drug. The duration and amount of flow varied; some patients had a heavy flow for as long as two weeks.

*Vaginal smear response:* Vaginal smears taken after the method described by Papanicolaou[13] have been used as an index of estrogenic effect in nearly all cases. We found it possible to make a rough but satisfactory estimate from immediate examination of the wet smear under a coverslip. A castrate type of smear, consisting of small round epithelial cells with large nuclei and many leukocytes (Fig. 1), is changed readily, by a small dose of stilbestrol, to one showing larger cells with a tendency to polyhedral form and smaller nuclei with a few or even no leukocytes (Fig. 2). A considerably larger dose is required sometimes to bring the smear to an approximately full estrus type, indicated by sharply polyhedral cells with small nuclei having no visible nuclear structure and the absence of leukocytes and debris (Fig. 3). The effective therapeutic dose frequently is less than that required to produce the latter type of

smear. It is probable in some cases, as noted by Shorr[9], that a dose sufficient to produce a full estrus smear cannot be given orally.

We feel that the wet vaginal smear should be regarded only as a rough index of estrogenic effect. If an approximate full estrus type of smear is produced without definite symptomatic relief, the symptoms are regarded as not being due to estrogenic deficiency. When a full estrus type of smear could not be correlated with the symptoms, such symptoms have not been those usually caused by ovarian failure.

Stains of fixed preparations, using the method of Papanicolaou[13] and later that of Shorr[14], have been made routinely in addition to the wet smears. The response as judged by vaginal smears attaining full estrus or slightly less than the full estrus type varies considerably.

The dose of stilbestrol necessary to produce full estrus or slightly less than full estrus response varies considerably in various individuals. It is influenced undoubtedly by the amount of estrogen in the body. In such cases as those illustrated in the following table a nearly complete or complete estrus response was obtained on doses of 2 mg. per day or less and in one on a dose as low as 0.25 mg. per day. The response is graded as 1+ to 4+ on a basis of 4.

TABLE 2

| *Case* | *Age* | *Diagnosis* | *Dose* | *Vaginal Smear Response* |
|---|---|---|---|---|
| 5 | 31 | Hypo-ovarianism | 1.0 mg. | 3+ |
| 12 | 37 | Premenstrual Headache | 2.0 | 3+ |
| 13 | 42 | Premenstrual Headache | 0.5 | 4+ |
| 16 | 44 | Castrate | 0.75 | 4+ |
| 17 | 35 | Castrate | 1.0 | 4+ |
| 21 | 50 | Menopause | 1.5 | 4+ |
| 26 | 40 | Menopause | 0.25 | 4+ |
| 30 | 57 | Menopause | 1.5 | 3+ |
| 33 | 47 | Menopause | 0.75 | 3+ |

*Previous therapy with natural estrogens:* Twenty-four of our patients received natural estrogens by injection before stilbestrol was given. All cases in which stilbestrol was tolerated obtained the beneficial effects of the natural estrogen. In some of these patients, stilbestrol was gradually substituted for the natural estrogen (usually estradiol benzoate) without symptomatic relapse. No constant dosage was noted in these.

*Toxic effects and complications:* Early in the study of stilbestrol

severe toxic effects including liver damage were reported to occur in animals.[15] Selye[16] demonstrated the same type of effect following the administration of large doses of natural estrogens. Clinically various unpleasant symptoms and complications have been reported following the use of stilbestrol, usually referred to as toxic effects, although there may be some doubt as to the propriety of the use of the term "toxic." These include nausea, vomiting, abdominal distress or pain, headache, dizziness, cutaneous rashes,[9] paresthesiae, toxic psychosis,[9] hematometra and hematocolpos,[17] and bloody diarrhea.[9] MacBryde,[12] Shorr,[9] and Buxton[18] have performed various laboratory tests including blood counts, urinalyses, blood chemistry and liver function tests following stilbestrol therapy. Aside from the development of albuminuria and casts in one case (Buxton) and some inconclusive changes in liver function (Shorr), all findings were normal.

In our series it was necessary to discontinue the drug because of unpleasant symptoms in five cases (12.5 per cent) and mild untoward symptoms occurred in six others (15 per cent). Three of our patients had severe nausea and two of these had vomiting. In all three, the drug was discontinued after one dose. In four there was mild nausea; one of these had nausea with the use of 0.5 mg. daily but maintained symptomatic relief and avoided nausea by reducing the dose to 0.25 mg. One patient who was taking 0.25 mg. per day had such mild nausea that she did not wish to discontinue the drug. In two patients, mild nausea was reported at the outset only. There may have been more cases in this latter class, for we frequently have refrained from suggesting the possibility of untoward reactions.

Two patients with anorexia nervosa and ovarian deficiency were able to take stilbestrol without any increase in their tendency to nausea. The greatest dose was 0.25 mg. four times daily. One patient had severe arterial hypertension with constant nausea. She took 2 mg. daily without any increase in the nausea.

The other "toxic" manifestations in our cases were headache in two patients, abdominal distress in one, and a hemorrhagic cystitis in one. The latter patient took 0.25 mg. of stilbestrol daily for one week on two occasions, and developed marked frequency and dysuria each time. A hemorrhagic cystitis was found on cystoscopy. Of these four patients, only one was able to continue the drug.

Conflicting reports have been made as to the avoidance of nausea by parenteral injection. That unpleasant symptoms may follow parenteral injection is demonstrated by case 30 cited above. Whether or not the nausea is a toxic reaction, there appears to be no good clinical grounds for considering it an indication of organic injury. Davis[4] gave 10 to 25 mg. of stilbestrol daily to three moribund patients for ten, thirty, and

forty-five days, respectively, and at necropsy could demonstrate no lesions attributable to this therapy. The lethal dose for animals has been found to be many times the effective therapeutic dose[12,16] while the dose required to produce nausea in patients often is near the therapeutically effective one.

While we draw no conclusions from this small series as to the relationship of size of dose to frequency or severity of effects, our impression is that the dose which will produce nausea sometimes is close to the therapeutically effective dose, and that it is wise to begin with small divided doses, and gradually to increase them in order that the therapeutic dose may not be inadvertently exceeded. Injections of natural estrogen may be used for more rapid relief at the beginning of therapy, although this often is not necessary. Since the nature of the so-called toxic effects is not understood, considerable caution in the use of the drug is warranted.

## Summary

Forty patients, including twenty-four cases of menopausal syndrome, fifteen of partial ovarian deficiency, and one of senile vulvovaginitis, have been treated with diethylstilbestrol. All of the patients who could tolerate the drug experienced improvement. "Toxic" effects were noted in eleven cases, six of which were able to continue the drug. In twenty-four patients who had previously received estradiol benzoate, stilbestrol reproduced the beneficial effects of the latter in all cases in which it was tolerated.

The use of small doses of stilbestrol at the beginning of treatment is suggested as a possible means of avoiding many untoward reactions.

## Illustrative Cases

*Case 5:* A thirty-one year old patient who had had a hysterectomy developed anorexia nervosa and lost weight to fifty-seven pounds. Estradiol benzoate and forced feeding brought her weight to eighty-eight pounds and strength and energy increased considerably. Vaginal smears changed from a markedly deficient to an approximately normal type. On withdrawal of estradiol benzoate, she experienced weakness, nervousness, and an increased tendency to headache and vomiting. A gradual change from estradiol benzoate to stilbestrol, 0.25 mg. four times daily, was made and symptomatic status and normal vaginal smears were maintained. No increase in the tendency to nausea was produced by stilbestrol.

*Case 11:* A thirty-five year old patient had a chronic left oophoritis and complained of scanty menstruation, severe mental depression, and hot flashes. Estradiol benzoate, 2000 R. U. (1/3 mg.) three times weekly, caused improvement in symptoms but did not abolish the hot flashes. Stilbestrol, 2 mg. daily, caused symptomatic improvement and relieved hot flashes but caused abdominal distress. A therapeutic oral dose of ethinyl estradiol caused nausea. Improvement was maintained without distress by giving 1 mg. of stilbestrol and 0.15 mg. of ethinyl estradiol daily.

*Case 12:* A thirty-seven year old patient complained of severe premenstrual headaches and a scanty menstrual flow. The symptoms were partly controlled on 0.25 mg. stilbestrol three times daily, and recurred on withdrawal. By gradually increasing the dose to 0.5 mg. four times daily the symptoms were controlled and the vaginal smears were brought to normal.

*Case 30:* A fifty-five year old patient with severe arterial hypertension, complaining of many and severe hot flashes for several years, required 50,000 rat units of estradiol benzoate daily together with testosterone propionate* for relief. On one occasion she was given 2 mg. of stilbestrol intramuscularly and exhibited nausea, malaise and stupor for thirty-six hours. At a later date she was given 0.25 mg. of stilbestrol orally daily, gradually increased to 2 mg. daily. This controlled hot flashes and caused no increase in a marked tendency to the nausea which she suffered.

* Oreton, Schering Corp.

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# NEUROCIRCULATORY ASTHENIA

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The problems of war and their effect upon the health of the people again are evident. The strong emotions engendered by war are certain to revive that condition which, common enough during peace times, was unusually prevalent during and following the last great war; namely, neurocirculatory asthenia.

Powerful emotional reactions stimulate the sympathetic and parasympathetic nervous systems, and cause well-known responses and sensations throughout the body. These subjective and objective reactions are generally recognized and accepted to be a comparatively normal but nevertheless variable physiologic accompaniment to a particular emotion; that is, hate, fear, patriotism, etc., induce distinctly different subjective feelings in the individual experiencing these emotions.

The systemic reaction to some of the more powerful emotions, such as fear, anxiety, worry, apprehension, despondency, etc., are unpleasant and annoying. Oftentimes these sensations excite further fear and anxiety and induce introspective thoughts. The pleasant emotional states are usually short lived, while the unpleasant sensations of some emotions may frighten the individual to the extent that still stronger reactions are induced, thereby causing a vicious cycle of fear—reaction, more fear—more reaction, etc. In this manner one can visualize the onset of the chronically unstable sympathetic nervous system, which is the fundamental pathological background giving rise to that vague clinical picture to which many names have been applied, but which is best known as neurocirculatory asthenia, hereinafter referred to as N.C.A.

The above theory serves as a working basis to explain the mechanism of N.C.A. Why some individuals are more susceptible to this annoying and distressing condition than others is not known. Certainly, everyone experiencing unpleasant emotions does not develop N.C.A.

Several factors probably play a role in conditioning this susceptibility. First is the marked difference in the personality of the individual as portrayed by the sympathetic response to his emotional reactions. If he is aware that these reactions also occur in others they are not so likely to cause fear in him. However, when the reactions are chiefly inward or subjective, and especially when they attract attention to some vital organ (the heart, for example), they are likely to excite fear. This is especially true in the timid, self-conscious, introspective person. Thus, a cycle may be started more easily in the introvert than in the extrovert.

The difference in the emotional behavior of individuals undoubtedly arises from a fundamental inherited difference in the germ plasm. Environmental conditions such as climate, nutrition, and disease, which

alter the physical state of individuals unquestionably change to some extent the true course of the originally inherited emotional pattern. Environment affecting only the psychic state appears to alter the degree and extent of the emotions rather than the fundamental pattern. In many instances too much emphasis is placed upon one environmental episode of a psychic nature as the explanation for functional disorders. The recognition of the state of the fundamental germ plasm is extremely important in the diagnosis and prognosis not only in N.C.A., but also in all functional states.

A less specific but equally important factor in determining the susceptibility to develop N.C.A. is the increasing evidence that the emotional state activates circulating chemical hormones to produce systemic accompaniments of reactions and sensations rather than a simple end-organ effect from a nerve impulse. If such is true, some individuals probably will produce relatively large amounts of these hormones with a trivial emotion while others may be unusually sensitive to a small amount of such hormones. I cannot refrain from comparing this to the allergic sensitization of individuals to a protein and the great variability of the shock organs to the same protein in different individuals and at different times.

The possibility of a vicious cycle formation is visualized better if we consider the possibility of a trivial emotional reaction causing the secretion of excessive amounts of hormones which circulate and act long after the emotion has ceased, and which cause the somatic reaction of the emotion to persist. A familiar example of this is the continued excitement state of the body which continues after a violent spell of anger has subsided.

The above explanations have been entirely theoretical and may contain no basic truths, but until we know more about N.C.A., this conception must serve in both the diagnosis and treatment of N.C.A. and many other functional disorders. Without this or a similar conception of the N.C.A. state, the physician cannot be of much help to these unfortunate individuals. Oftentimes these patients are better off in the hands of those who practice the art of healing with little scientific knowledge, than in those of men better equipped with scientific knowledge but lacking in the art of medicine.

## Diagnosis

To those familiar with the diagnosis and management of functional problems, the diagnosis of N.C.A. is simple in most cases, merely made by a quick glance at the facies, a handshake, and a few simple questions to analyze the personality of the patient. However, to those who believe that all bodily disturbance must be explained on the basis of organic

disease, the diagnosis proves difficult and attempts to treat suspected causal conditions only serve to make the patient worse.

To those familiar with the syndrome, a discussion of N.C.A. is unnecessary, and to those who are not familiar with it, this article will prove of little value because any effort to present a word description of this kaleidoscopic clinical picture is totally inadequate. A total description of the tremendous variations of this syndrome would be confused with so many disease states that again it would fail in its purpose. Therefore, I shall confine my remarks to the cardinal features of the typical cases because one or more of these features will be present in nearly every case. If one learns by experience the less obvious features associated with the obvious, the diagnosis of the unusual case becomes less difficult.

A patient will present himself with a story of multiple complaints out of proportion to any one disease process. His chief symptoms will be nervousness, fatigue, heart consciousness and palpitation, and nearly always some form of gastro-intestinal disturbance. His nervousness is of the stage-fright type, always aggravated by situations which cause self-consciousness. If there is no evidence of an anxiety state, the diagnosis must be made with a great deal of hesitation. The other symptoms mentioned above are not so pathognomonic.

Other suggestive symptoms are tremor, peculiar feelings in the head, dizziness of the vasovagal type, photophobia and aching eyes, globus hystericus, sighing respirations, syncopal attacks, all varieties of gastro-intestinal disturbances, all varieties of peculiar somatic sensations, excessive perspiration, frequency of urination, disturbed fears concerning sex and peculiar sensations about the genitalia, and many other complaints too numerous to mention.

The patient usually is in the teens or early twenties. If seen at an older age, his symptoms usually will have started at this early age. Males always predominate slightly, but the ratio increases enormously in war times because of re-adjustments in life.

The hand is moist, sometimes dripping with perspiration, frequently cold, but occasionally quite warm. The hands and feet are beefsteak red in color with a sharp delineation at the wrists and at the ankles. As the patient sits stripped for examination, a stream of perspiration trickles from his axilla. A most characteristic sign is the brilliant dark brick red color of the ears and lips due to capillary dilatation and stasis. The pupils are dilated. A coarse intention tremor frequently is present. The pulse usually is rapid and sinus arrhythmia is present. The systolic blood pressure is elevated slightly and the diastolic pressure is low. The increased pulse pressure often is sufficient to cause a capillary pulsation beneath the nails. The pulse and blood pressure alter quickly with exercise, position, and bed rest. Sighing respirations are observed and

the patient complains of effort to get a deep breath. The abdomen may or may not show diffuse tenderness. The colon may be spastic and may cause "right-side-itis" for which the appendix frequently is removed, without relief.

The outstanding features of the examination are the unstable vasomotor system, the excessively moist hands and axilla, and the red ears and lips. In conjunction with a self-conscious introvert personality and a host of subjective symptoms the diagnosis should be obvious. However, in spite of many fundamental differences in the clinical picture, this condition frequently continues to be confused with hyperthyroidism. It is true that there are many symptoms common to the two diseases to make them superficially similar, but there are so many distinguishing features that there is rarely any question as to the true nature of the disease. I have seen a few young individuals with a characteristic picture of N.C.A. who also developed hyperthyroidism. Relief from the latter was obtained by surgery but the symptoms of N.C.A. continued without change.

Palpitation and tachycardia, nervousness, tremor, weakness, and loss of weight are common to the two conditions and yet in each there is a clinical difference. The palpitation and tachycardia of N.C.A. is associated chiefly with effort and excitement, and quiets down with bed rest. In hyperthyroidism it is more constant and sustained, and responds much slower to bed rest.

The nervousness is different in each condition. In N.C.A., it is a feeling of apprehensiveness. The patient almost invariably will reply in the affirmative if asked the leading question, "Is your nervousness similar to that of stage fright?" The nervousness of hyperthyroidism is like an uncontrolled inner stimulation and is not so definitely related to fear and anxiety.

The tremor is slightly different but not enough to be of differential value.

The weakness is entirely different. N.C.A. is like neurasthenia, while hyperthyroidism causes a weakness characteristic of the exhaustion of actual organic disease. The patient with N.C.A. loses weight because he does not eat; the patient with hyperthyroidism loses weight in spite of satisfying a ravenous appetite. Anorexia is unusual in hyperthyroidism; the rule in N.C.A. If in N.C.A., the appetite is good, there is a tendency to quick satisfaction and an early feeling of fullness.

Goiter may be present in both conditions, but in N.C.A. it will be a soft colloid type, or a small adenoma. A symptom that causes more confusion than any other is the common symptom of feeling a lump or tightness in the throat, to which the term "globus hystericus" is applied. Characteristic of the anxiety tension state and rarely, if ever, present in

hyperthyroidism, except where complicated with thyroiditis, globus hystericus unfortunately directs the patient's attention to the thyroid region. If in addition the N.C.A. patient has a small colloid goiter, he becomes very susceptible to the idea of hyperthyroidism and consequent surgery. As a general rule, a subjective feeling of discomfort in the neck always should steer the cautious physician away from rather than towards the diagnosis of hyperthyroidism. His surgical results will be much the same as those from the removal of the appendix in chronic right-sided pain.

True exophthalmos, of course, is pathognomonic of hyperthyroidism. This should be measured because the wide palpebral fissures of a frightened person are very confusing. The individual who inherits large protuberant eyes also offers some confusion. The patient or a life-long friend, however, usually is able to tell whether or not there has been a change in appearance. The physician seeing the patient for the first time might be confident that true exophthalmos exists.

The basal metabolic rate has not been emphasized in the differential diagnosis because, while helpful if interpreted properly, it often may be more confusing than otherwise. Agitated, frightened, N.C.A. patients frequently have a high rate of from plus 12 to plus 20. This, of course, is not a basal rate. Only after two to four readings by the same technician is it possible to get satisfactory relaxation. Sometimes the patient consults or is referred to another physician for opinion. The new atmosphere may again raise the rate. While several rates may be high, if done in different places they are consequently of little value. If, clinically, the patient has N.C.A. a moderately elevated basal metabolic rate should not influence the physician's clinical judgment.

The most difficult problem that confronts one from a diagnostic standpoint is to feel confident that exhaustive conditions such as early subclinical tuberculosis, undulant fever, the rheumatic state, focal infection, endocrine disturbance other than thyroid, primary myasthenias, and a host of others have not been overlooked. Fortunately, these conditions rarely simulate N.C.A., but they may coexist and add an additional drain to the patient's energy, interfering seriously with therapeutic efforts. The problem of coexisting disease is especially difficult in the patients with N.C.A. brought in by parents to find out why the child cannot carry on a normal routine without the fatigue. The parent usually insists that it must be disease, will not accept N.C.A. as a diagnosis, and insists that a thorough search must be made for disease, usually with failure. Even if mild coexisting conditions are found, their treatment helps the fundamental condition very little. The whole problem of N.C.A. strains the relations of the patient, and especially the relation of the patient's family with the physician. This attitude of the parents is also unfortunate

in respect to the patient because they often are unwilling to cooperate in a rational therapeutic regimen.

## Treatment

It might truthfully be said that no specific medical treatment can be considered to have any effect upon this condition. Treatment of the annoying symptoms helps to halt the vicious cycle. Psychotherapy through instillation of confidence, while difficult to evaluate, certainly appears to be the most important treatment in this disease. Time, the great healer, is slow but certain in eradicating most of the signs and symptoms of this disease of young people. While the endocrine approach would certainly seem promising, the efforts in this direction are not encouraging either through depression or stimulation of the functions of the various glands. Drugs having a particular action on the sympathetic nervous system have been most disappointing and exert little effect in stabilizing this feature of the disease. At the best, they bring occasional symptomatic relief.

Until more specific methods are available the treatment of these cases should be approached in the following way after the diagnosis is established satisfactorily.

A long talk with the patient is necessary to impress him with the fact that all his symptoms are due to an emotional upset of the sympathetic nervous system. This is relatively easy because the patient immediately realizes that all of his symptoms are like stage fright. Time, however, must be spent in dissipating specific fears, especially those about the heart. More than one session with the patient is necessary to remove fears and restore confidence. The mechanism of the vicious cycle and conditioned reflexes should be explained because the patient cannot understand why he should have symptoms when he consciously has nothing to fear. Explanations always should be in simple language that the patient can understand and similes and analogies are most helpful in illustrating points. High sounding medical terms only confuse the patient further. Any psychic twists, especially about sex and the sex habits of the young, should be discussed frankly and fears relieved. It is inadvisable to attribute this condition to perverted or solitary sex habits.

These patients frequently are ambitious and their ambitions are thwarted by their poor endurance. Efforts to reconcile their points of view in regard to overambition should be made. Competition and striving should be discouraged.

The enormous requirements for physical rest must be emphasized. Most of these patients do unusually well on ten hours of bed rest, but seldom get along well on less. Morning sleep is especially valuable.

Efforts should be made for them to join social groups gradually and to cultivate poise and confidence. Taking courses in public speaking, joining athletic groups, and attending church groups are especially good. Caution must be used to keep them from rushing into this too fast, or this type of treatment will prove detrimental.

Early marriage with a socially inclined mate is most helpful. When N.C.A. persists into later life, as it does occasionally, it is not unusual to find that many of these patients never have married. Which is cause and which is effect is unanswerable.

It is impossible to discuss adequately all the ways and means necessary to employ in every case to build up confidence and to allay the fear that keeps the cycle going. Unless a great deal of time is given to this phase of treatment, results are hopeless. The change that comes over these patients during and for a short while following a confidence inspiring talk is frequently amazing. A simple discussion of their troubles helps them to understand and this understanding is most vital to dissipate fears.

A very simple and effective method of treatment in relieving the annoying vasomotor symptoms is to urge the patient to do brisk calisthenic exercises for ten minutes, endeavoring to bring out a good sweat, using adequate clothing during the exercise if sweating is difficult. Following this, he should take a cold shower immediately or plunge into a tub of cold water previously drawn. Long and hot baths should not be taken as they cause further peripheral vascular dilatation. Following the cold plunge, the patient first dries in the usual manner, and then rubs himself with a dry, rough Turkish towel until the skin begins to glow. Following this, a thirty-minute period of relaxation should be taken. Usually the patient will report a surprising amount of improvement after following this procedure for thirty days. Treatment should be undertaken at least daily and preferably twice daily. At the start the patient often resents this drastic water cure and frequent urging to continue is necessary. If play and relaxation in a gymnasium can be incorporated with the above treatment, it is much better.

The use of medicine should be avoided as much as possible and the patient should be encouraged to believe he is not ill and, therefore, does not need medicine. Occasionally, however, sedation is necessary for extreme nervousness and insomnia. Treatment of gastro-intestinal symptoms frequently will require a brief period of medication.

It is important to relieve annoying symptoms as well as to explain their benign character because nothing is so reassuring as their disappearance.

With each slight improvement the patient gains more confidence and the course of treatment of N.C.A. can be shortened in this manner. In

some, N.C.A. can be prevented from becoming chronic, because if the condition still is present in patients over thirty-five years of age there is not much encouragement. Occasionally because of severe psychic insults resulting in tremendous loss of self-confidence, the disease will start in later years. If recognized early and if proper treatment is applied, it is short lived; otherwise, it presents a most difficult problem.

One difficulty in handling these patients is to find an adequate amount of time to give them. Good results are proportional to the time spent with them. Visits should be frequent. If too much time elapses between visits, the patient becomes discouraged, loses the benefits obtained, loses confidence, and goes elsewhere or entirely ceases efforts to obtain help. Engaging the help of the minister, teacher, or layman whom the patient respects often relieves the busy physician of some of this responsibility to these patients.

## Conclusions

N.C.A. is an important subject. Futures may be completely changed by the advice the young N.C.A. patient receives. It is a subject worthy of our best efforts, especially now when many of our young men are experiencing the fearful emotions that go with war.

An attempt has been made to present a clinical approach to the diagnosis and treatment of the difficult problem of N.C.A.

# RECENT DEVELOPMENTS RESULTING IN AN INCREASING OPERABILITY RATE FOR CANCER OF THE STOMACH

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Although little has been contributed to the technical aspects of gastric surgery since the days of Billroth, Hoffmeister, and Polya, developments in the past two years have enabled us to double the operability rate of cancer of the stomach and to reduce simultaneously the mortality rate to nearly half of its previous figure. Since 1938 the number of gastric resections for cancer of the stomach at the Cleveland Clinic has risen from 15 per cent to 30 per cent of all cases seen. At the same time the mortality rate for these operations has fallen from 25 per cent prior to 1939 to 15 per cent in the thirty-three cases having resections in the past two years. If cases requiring total gastrectomy or modifications of this procedure entailing esophago-gastrostomy or esophago-enterostomy are excluded, the mortality rate in partial gastrectomy for cancer of the stomach has been reduced to 7 per cent.

These results have not been obtained as a consequence of technical advances in gastric surgery, nor are they the result of earlier diagnosis. The widening of operability and the lowering of the mortality rate are, I believe, largely the result of the use of sulfapyridine, and of improvements in the technic of anesthesia.

Prior to 1939, the vast majority of gastric resections for cancer were performed under ether anesthesia, and the incidence of postoperative pneumonia was high. Fifty per cent of the postoperative deaths in this period resulted from pulmonary complications. With the use of sulfapyridine, pneumonia can be prevented or cured, and the mortality rate of gastric surgery reduced.

In subtotal gastrectomy for advanced carcinoma, even when the patient is anemic, emaciated, and in poor condition, the danger of peritonitis is slight. The greatest danger always has been pneumonia. Since this complication now can be avoided or treated successfully, the surgeon may feel safe in performing radical gastrectomies in elderly patients who would not have been expected to survive in the days before the development of sulfapyridine and sulfathiazole. These changes have necessitated a revision of our standards of operability for cancer of the stomach.

The prognosis of patients with cancer of the stomach always has been poor. Only a small percentage of all patients subjected to resection of the stomach for cancer have lived five years without recurrence. In spite of this, perhaps no operation is attended by more brilliant initial results than gastric resection for carcinoma.

The patient who prior to operation had continuous gastric distress,

who was anemic, could not eat, and had lost 30 to 40 pounds in weight, often is transformed by partial gastrectomy to a healthy-looking, comfortable individual. Even though he may harbor carcinoma in the retroperitoneal glands or in the liver, he is given a year, two years, or three years of comfort and well-being before succumbing to metastases. Such palliation of symptoms is well worth while and is desirable because both patient and physician can live in the hope that the disease may have been eradicated completely.

If these results can be obtained without subjecting the patient to too much risk of postoperative death, both surgeon and physician are happy that palliation and a chance of cure can be afforded. However, if the risk of operation is considered great, and even though the patient is willing to assume that risk, the surgeon and physician are loath to assume the responsibility.

A hospital death always is unwelcome and, for this reason, patients with advanced carcinoma of the stomach or aged patients who were not good operative risks were rarely subjected to radical gastric resections. With the lowering of the operative mortality in gastric surgery, there should be a widening of the standards of operability, and many more patients should be given palliation of their symptoms and a chance of cure by gastric resection.

A second factor of value in the management of the bad risk case has been the increasing use of local anesthesia. Although the use of local infiltration anesthesia and a splanchnic block is by no means new, only recently with the development of the short action barbiturates designed for intravenous use has local anesthesia become satisfactory to both patient and surgeon.

A gastric resection does not require deep anesthesia and absolute relaxation. In fact, local anesthesia with its quiet respiration and absence of straining is often preferable to the deepest general anesthetic. The use of sodium pentothal, given as an *analgesic* agent in conjunction with infiltration of the abdominal wall and splanchnic region with novocaine, results in comfort to the patient and affords a quiet relaxation which is ideal for the surgeon. The depression of a general anesthetic agent is obviated; hard breathing and inhalation of mucus is avoided; the blood pressure is not depressed such as in spinal anesthesia; and the patient's nervousness and discomfort is controlled at will by adding additional small amounts of pentothal. Two or 3 cc. of a 5 per cent solution of sodium pentothal given slowly will result in a quiet analgesia characterized by a complete absence of excitation or euphoria. The patient becomes drowsy and may fall asleep, but is always easily roused. If he complains of discomfort, an additional 1 or 2 cc. may be added. As a rule, 10 cc. will suffice to complete a gastric resection.

In the majority of cases, the abdomen can be opened without discomfort under local anesthesia. Following this, the patient is given 3 or 4 cc. of pentothal and the splanchnic region is infiltrated with novocaine. The tumor then is delivered and resected. During the suturing of the lines of anastamosis there is rarely any discomfort. Only during periods of traction on the stomach or mesentery does the patient experience any discomfort, and at these times the addition of small amounts of pentothal quickly allays all pain. A small additional dose often will facilitate closure.

Only the very nervous individual fails to react satisfactorily to this

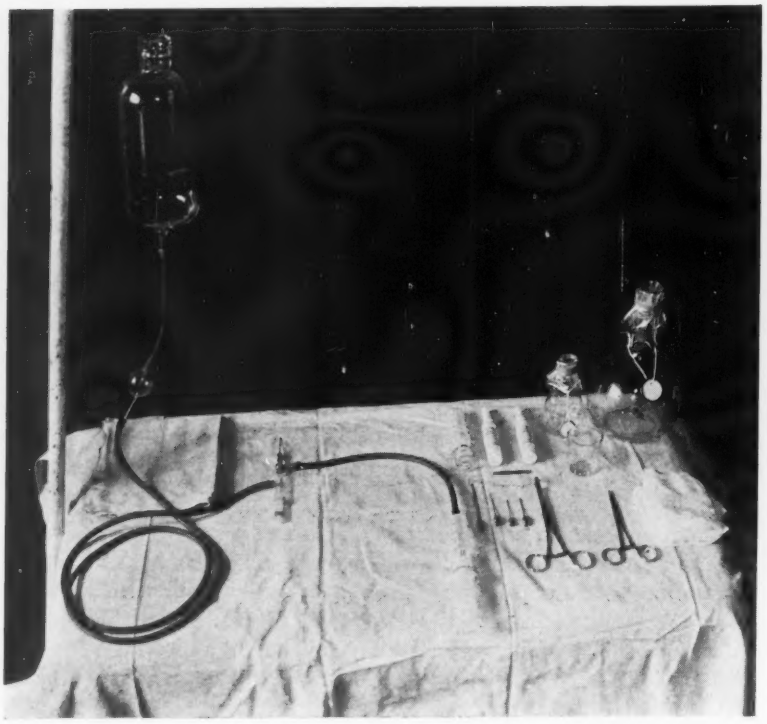

FIGURE 1: Apparatus for intermittent administration of sodium pentothal during abdominal operation.

type of anesthesia. If the patient continues to complain, it probably is better to give 3 or 4 cc. of pentothal as an aid to the induction of a general anesthesia rather than to give large doses of this drug (Fig. 1). I wish to emphasize that *pentothal is recommended as an analgesic, not as an anesthetic agent* for prolonged abdominal operations.

With the increasing use of local anesthesia, and with the early use of

sulfapyridine or sulfathiazole in the prophylaxis and treatment of pneumonia, we not only have extended the scope of operability to older patients and to patients with greater degrees of anemia, debility, and emaciation, but also have undertaken a higher percentage of gastric resections upon patients having lesions high in the cardia, or involving adjacent organs by direct continuity. The following case reports illustrate some of the more hazardous technical procedures which have been carried out by this technic.

*Case 1:* Total gastrectomy for infiltrative carinoma of the stomach.

*History:* The patient was a forty-four year old man who had experienced burning upper abdominal pain for three months prior to entry. He had lost ten pounds in weight.

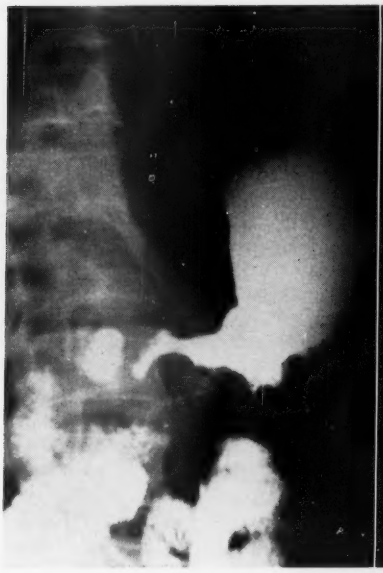

FIGURE 2: Roentgenogram showing extensive infiltrating carcinoma of the stomach requiring total gastrectomy.

FIGURE 3: Postoperative roentgenogram showing esophago-enterostomy following total gastrectomy for carcinoma.

Physical examination revealed no abnormalities. Roentgen examination of the stomach showed an extensive filling defect in the distal two thirds (Fig. 2).

*Operation:* Under local anesthesia, supplemented by nitrous oxide oxygen and ether, the abdomen was explored. Exposure was obtained by cutting the costal cartilages of the lower ribs on the left and reflecting the costal cartilage upward, care being taken to avoid opening the pleura. The ligament of the left lobe of the liver also was cut close to the diaphragm and the left lobe of the liver was retracted. Excellent exposure of the esophagus was thus obtained. The

entire wall of the stomach from pylorus to esophagus was thickened. Several lymph glands along the lesser curvature were enlarged and hard. The jejunum was brought up through a rent in the mesocolon and anastomosed to the posterior wall of the esophagus by a row of interrupted silk sutures. The entire stomach then was resected. The anastomosis was completed by a row of continuous catgut sutures both anteriorly and posteriorly and by a row of interrupted silk sutures anteriorly. Finally, the diaphragmatic and esophageal peritoneum was mobilized and sutured over the line of anastomosis to the jejunum with interrupted silk sutures. An entero-anastomosis was performed, and the abdomen was closed without drainage.

*Course:* The immediate postoperative course was stormy, the patient's temperature rising to 104° F. and pulse rate rising to 140 on the first postoperative night. In response to sodium sulfapyridine given intravenously, the temperature and pulse reaction subsided. A roentgenogram of the chest revealed bronchopneumonia. By the tenth postoperative day, the temperature and pulse had fallen to normal levels. After removal of the nasal tube which had been inserted before operation and which was kept in the jejunum during the first week, he was able to swallow food and fluids without discomfort. The patient was discharged on the eighteenth postoperative day. A roentgenogram taken one month after operation showed the barium entering the small bowel without obstruction (Fig. 3). The patient, however, has failed to gain weight in a satisfactory manner and still has some abdominal distress, possibly the result of metastasis, although no evidence of distant metastasis was found at the time of operation. In view of the diffuse infiltration of the lymph glands the prognosis is poor.

*Pathological Report:* The wall of the stomach was diffusely thickened and edematous and the mucosa was diffusely hemorrhagic. There was an irregular ulcer, 2 cm. by 3 cm. in diameter on the lesser curvature and extending into the anterior and posterior walls. There were numerous enlarged lymph nodes on both lesser and greater curvatures, but these were soft and not suggestive of metastatic carcinoma.

*Microscopic Examination:* A section from the ulcerated area showed highly undifferentiated adenocarcinoma infiltrating all coats of the stomach and extending into the omental fat. A number of lymphatics were filled with tumor cells. A section taken near the greater curvature showed the mucosa to be intact, but the submucous coat was diffusely infiltrated with carcinoma. Sections of two omental lymph nodes showed diffuse involvement with carcinoma.

*Comment:* This type of carcinoma of the stomach probably offers the poorest prognosis as to longevity and possibility of permanent cure. When the carcinoma has disseminated itself through the lymphatics and has diffusely invaded the lymphatic channels, the chances of removing the entire growth are minimal. The most favorable cases are those in which there is a definite localized tumor without infiltration of the lymphatics or extensive lymph note metastasis.

*Case 2:* Lymphosarcoma of stomach; esophago-enterostomy with preservation of a portion of the fundus.

*History:* The patient was a fifty-two year old man who complained of epigastric pain of one year's duration. He had lost twenty pounds in weight and the symptoms had increased in severity despite the use of a modified Sippy diet.

The physical examination was essentially negative. Roentgen examination of the stomach showed an extensive filling defect with infiltration of the walls of the entire pars media and extending into the pars pylorica of the stomach.

*Operation:* Under local and splanchnic anesthesia supplemented with

sodium pentothal and nitrous oxide analgesia, the abdomen was explored. There was a firm neoplasm involving the entire lesser curvature of the stomach from pylorus to esophagus. A few large firm glands were palpable in the mesentery along the lesser curvature. Since the greater curvature of the stomach was not involved, it was decided to resect all of the lesser curvature and to leave a portion of gastric mucosa on the side of the greater curvature to increase the capacity for food. The entire lesser curvature and the greater part of the stomach on the greater curvature then was resected. The esophagus and a portion of the fundus were anastomosed to the jejunum by the posterior Polya technic. Because the jejunum was carried so high on the lesser curvature side, an entero-enterostomy was performed.

*Course:* The postoperative convalescence was uneventful. The patient left the hospital on the fourteenth postoperative day. Five weeks after operation he

FIGURE 4: Lymphosarcoma of the stomach.

had gained seven pounds. He stated that his appetite was very good and that he was free from pain.

*Pathological Report:* The specimen consisted of a large part of the stomach, including the pyloric ring and very little of the duodenum. On the lesser curvature there was a very large, irregular, ulcerated lesion measuring 8 cm. longitudinally and 8.5 cm. transversely. The margin of the ulcer was outlined by hyperemic mucosa which was not thickened and was slightly overhanging. The ulcer extended to this outlined margin. The base of the ulcer was covered by a thick layer of plastic exudate. The wall of the stomach was considerably thickened at the site of the ulcer and there was quite marked induration of the fat of

the lesser omentum. There were numerous considerably enlarged, lesser omental lymph nodes. On the anterior wall there was another small ulcer 1.5 cm. in diameter similar in gross characteristics and extending to the muscular coats. On the posterior wall just beyond the distal border of the large ulcer there was another early ulcerated lesion 1.5 cm. in diameter (Fig. 4).

*Microscopic Examination:* Sections of the stomach showed ulceration with complete loss of mucosa and a lymphosarcomatous growth involving the submucous and mucous coats chiefly, but also involving the muscular coat in some areas. Sections of numerous lesser and greater omental lymph nodes showed lymphosarcomatous involvement.

*Comment:* Several patients with lymphosarcoma of the stomach have done well following gastric resection alone and others have responded favorably to roentgen therapy. If a recurrence of the tumor occurs in this case a course of roentgen ray therapy will be given.

*Case 3:* Extensive carcinoma of stomach with direct extension of tumor into the pancreas and liver; gastric resection.

*History:* The patient was a fifty-seven year old man who gave a history of anorexia and vomiting of eight months' duration with a loss of twenty-five pounds in weight.

Physical examination was essentially negative, except for the finding of a large, hard epigastric mass. Roentgen examination of the stomach showed a large filling defect involving the entire pars pylorica.

*Operation:* Under local anesthesia with a splanchnic block, the abdomen was opened and the stomach exposed. The lesion involved the entire lower half of the stomach, and the left lobe of the liver by direct extension. It was fixed posteriorly to the pancreas which also had been invaded by direct extension of the tumor. In spite of the extensiveness of the local lesion, the omental lymph nodes were not very much enlarged and no nodules were palpable in the liver. Resection of the lesion, therefore, was decided upon. The portion of the liver invaded by the carcinoma was about two inches in diameter and after electrocoagulation of the liver tissue this area was resected along with the carcinoma. There was no bleeding and no apparent leakage of bile. Because the body of the pancreas had been similarly invaded, the anterior surface of this organ likewise was resected with the primary lesion. The stomach was anastomosed to the jejunum by the posterior Polya technic. Two rubber tissue drains were left in the pancreatic bed.

*Course:* The postoperative course was uneventful except for the development of a pancreatic fistula which discharged large amounts of clear fluid, but showed no tendency to digest the skin. The patient left the hospital on the eighteenth postoperative day and was eating well without distress. Two months later he had gained fifteen pounds, and he stated that he never felt better in his life. The fistula closed spontaneously one month after operation.

*Pathological Report:* The specimen consisted of the distal end of the stomach in which there was a large tumor mass with a central irregular ulcer 7 cm. by 13 cm. in diameter. All coats of the stomach were infiltrated by the tumor and were from 2.5 to 3 cm. in thickness. Attached to the lesser curvature was a piece of liver tissue 3 cm. in diameter and 1 cm. in thickness.

*Microscopic Examination:* Sections of the tumor showed a highly undifferentiated adenocarcinoma infiltrating all coats of the stomach and extending into the mesenteric fat. Of the thirteen lymph glands examined, only two were involved by metastasis.

*Comment:* In spite of the fact that this tumor is highly undifferentiated and infiltrating, the absence of extensive lymph node involvement makes the prognosis better than that in Case 1, in which lymph nodes, lymphatics, and the entire gastric wall were diffusely infiltrated. A similar case of a large, highly undifferentiated, infiltrating carcinoma of the stomach involving the liver by direct extension was subjected to gastric resection over a year ago, and the patient is still gaining weight, eating well, and is free from symptoms.

## SUMMARY

1. The operability of carcinoma of the stomach has been doubled and, at the same time, the mortality rate has been nearly halved.

2. This improvement in operability and mortality figures is attributed largely to advances in anesthesia and to the control of postoperative pneumonia with sulfapyridine and its derivatives.

3. In view of the diminished operative risk, we believe that the operability rate of carcinoma of the stomach should be further increased. In this way, palliation and a chance of cure will be afforded to many patients with carcinoma of the stomach who, in the past, have been considered to be inoperable.

4. A case of lymphosarcoma of the stomach, a case of carcinoma of the stomach with direct extension to the pancreas and liver, and a case of carcinoma of the stomach in which total gastrectomy was performed are reported.

# UVEITIS

A. D. Ruedemann, M.D.

The diagnosis of uveitis, especially of the low-grade recurring type, is one of the most exacting problems in medicine. Difficult to diagnose, difficult to treat, and offering a very poor prognosis, uveitis comprises one of the largest groups of ophthalmological cases. Few persons, other than the ophthalmologist, appreciate the loss of sight from this disease and its economic cost.

Uveitis may occur in two forms: (1) the acute exudative type which may be rapid and severe, or rapid and short-lived, and (2) the low-grade recurrent type which may present itself in recurring severe attacks, recurring mild attacks, persistent severe attacks, or persistent insidious mild attacks. Differentiations also may be made as to the portion of the eye attacked, i. e., the iris, ciliary body, or choroid. The involved part usually is attacked repeatedly. Because the attacks recur, uveitis presents a serious problem, and requires painstaking effort and skill in diagnosis and treatment. Yet, the prognosis must be guarded. The patient must be informed of his condition and must be studied from a physical standpoint, as it is inadequate to treat him locally and not generally as well.

The etiology of chronic uveitis may be classified as follows:

Group 1.—Uveitis due to foci of infection in the tonsils, teeth, prostate, cervix, gastro-intestinal tract, gall bladder, sinuses, etc.

Group 2.—Uveitis due to low-grade general infections, tuberculosis, syphilis, and undulant fever.

Group 3.—Uveitis associated with deficiency diseases, vitamin deficiency, diabetes, hypothyroidism, and allergy. Also in this group may be included diseases associated with other faulty body function such as gout, arthritis or rheumatism, and vascular degeneration.

Group 4.—Traumatic uveitis secondary to penetrating wounds which either are accidental or surgical, or due to contusion of the eyeball. The latter need not be extremely severe.

It sometimes is possible to refer the cause of the uveitis to one of these sources, but it is never possible to dismiss the problem after a single cause has been found. The inflammation may be classified from information gained from the history and physical examination, but the final diagnosis should not be made until the results of essential laboratory procedures have been well studied.

In Group 1, the tonsils and teeth are responsible for the condition in 60 per cent of the cases. Foci of infection from the prostate or cervix rarely play a role. However, the prostate in men thirty-five years of age or over, or the genital tract in married women or women with children may sometimes be the source of the infection. Foci of infection from disturbances

in the gastro-intestinal tract include those from infectious processes, and those from associated deficiency diseases.

Tuberculosis is the responsible factor in the largest number of cases in Group 2. It is a frequent etiological factor either because of a rare invasion of or because of an allergic sensitivity to the organism. Low-grade recurring attacks must be treated carefully over a long period of time. Syphilis is a relatively uncommon cause, but occurs with sufficient frequency to warrant a routine examination of the blood. Undulant fever is a recently discovered factor and is responsible for the disease much more commonly than was heretofore suspected. In approximately 125 cases of undulant fever, seven had the chronic uveal type of eye involvement.

In Group 3, the most common etiological factor is arthritis, or rheumatism, when the history and physical findings are positive for arthritis and no other cause is found. Parathyroid tetany and hypometabolism are factors in low-grade uveitis, as indicated by the formation of cataracts associated with anterior uveitis. Cases with a previous history of thyroid disturbances which necessitated surgery must be suspected of metabolic disturbances until proved normal. Mild and severe diabetes may be associated with disease of the uveal tract, and also must be studied and treated carefully. Sometimes associated with vascular disease is a low-grade degeneration of the uveal tract, probably caused by a local anemia, edema, or recurring hemorrhages. No other cause may be found and, although the progress is very slow, severe vitreous degeneration may result in much loss of vision. Some cases of retinal detachment probably belong in this group.

Frequently, there may be several causes for the uveitis. In an individual with more than one source of infection each source must be considered and treated in its relative importance. This is especially true in the acute fulminating types of uveitis in which time is an important factor. In low-grade chronic insidious uveitis, more time can be taken to remove the various sources of infection, and to watch the results of general therapy.

In the Group 4 cases, trauma, either penetrating or the product of severe contusion to the eye, may cause a progressive chronic type of uveitis which will destroy not only the sight of the eye involved, but also that of the other eye. An eye still retaining a foreign body from a penetrating wound must be under constant observation, and at the first sign of degeneration of the opposite eye, the offending eye must be removed, although in some instances it may be too late. Sometimes it is possible to treat those secondary to contusion and retain the globe, although cases have been seen in which the contusion has resulted in chronic degeneration of the globe, with the possibility of the production of a sympathetic ophthalmia.

To the accidental cases must be added cases of post-surgical uveitis. In every instance in which the iris or ciliary body is involved in surgery, there is a possibility of producing low-grade uveitis. This is especially true in cataract surgery if the base of the iris is partially incarcerated in the wound. Gradual degeneration of the globe may take place over a long period of time post-surgically, and the only possible cause is the surgical procedure itself. Fortunately these cases are rare, but this possibility must be kept in mind.

In treating uveitis, the local lesion first must be adequately treated and watched constantly for any change in the appearance or the type of inflammation. For example, a low-grade chronic iritis sometimes flares up suddenly and produces a severe secondary glaucoma which must be treated immediately. Local treatment is important only for maintaining the integrity of the eye. It is extremely important to treat these patients generally and to bring them to the best state of health possible. In many instances radical, aggressive procedures are essential to stop the progress of the eye lesions, as procrastination usually results in the loss of vision or the loss of an eye.

We have secured excellent results in many cases with the cooperation of the Department of Medicine. In order to trace the infection to its source, complete examinations are necessary. The amount of free hydrochloric acid in the stomach is determined by gastric analysis; roentgen examinations of the gastro-intestinal tract show the condition of the colon and determine the possibility of infection or disturbing pathology; stool examinations are made to determine the presence of any low-grade bacterial or parasitic infection in the gastro-intestinal tract. In the medical department, the patients are treated as the results of the examination indicate. The absence of free hydrochloric acid in the stomach may necessitate giving the patient hydrochloric acid with the addition of vitamins A and B, and the regulation of the diet. In certain cases, some patients have a habit of taking either a daily cathartic or an enema. This detrimental procedure may be a secondary factor and must be discontinued.

General physical factors are more important than local areas of infection. As a rule most patients have all foci of infection removed but the local condition in the eye persists. In this event, it is necessary to find some general condition to account for the recurring disease. From the gastro-intestinal point of view, it is essential to regulate the diet and the bowels, and to minimize the amount of alcohol intake. In order to retain and maintain normal weight, the caloric intake is regulated. It may be necessary to hospitalize some of these cases in order to institute proper treatment. While in the hospital, any infection in the teeth, tonsils and other similar sources should be removed. In addition to general medical treatment, local lesions in the eyes must be constantly watched for and

treated. One of our patients had a chronic osteomyelitis which was the source of the infection in the eyes. The osteomyelitis was treated successfully, but because of the condition of the eyes, local treatment was necessary over a long period of time.

In some cases of chronic rheumatism, it is necessary to hospitalize the patient and give a course of typhoid vaccine therapy. The attacks may be controlled, although in some instances a minor attack which is not as prolonged or as severe as the first attack recurs at a later date. Sometimes the recurrences gradually subside and disappear. However, in conjunction with typhoid therapy, such patients must be given general management and should be taught to care for themselves.

In the more chronic group of infections, such as tuberculosis, the patient must be treated from a general standpoint and, whenever possible, be given a long course of old tuberculin therapy. This therapy, with rest and a high vitamin diet, gives the best end result.

Patients with syphilis usually require careful and prolonged treatment and, as a rule, can be given a better prognosis than those with tuberculosis. In indulant fever, a recently discovered cause of uveitis, treatment is not as successful as in either tuberculosis or syphilis. Even though vaccine treatment may be used, the progress of the lesion is not halted as easily as in tuberculosis, and destruction of the eye appears to be greater than in either tuberculosis or syphilis.

Local treatment of the uveitis depends upon the part of the eye affected. It may be necessary to alternate the use of atropine with eserine, especially where there is degeneration of the pigment, as the tension of the eye tends to rise and routine treatment cannot be followed in all cases. Treatment must be prolonged and the individual may develop an idiosyncrasy to the drug, and other substances must be used to offset the local irritation. Fair consideration must be given to the drug used. It is extremely important to instruct the patients not to use more drops than are necessary. The excess drug may cause severe local irritation of the skin of the face, which will necessitate discontinuing its use. This is especially true following the use of atropine which is the best drug to use in treating iritis. Instead of atropine, it may be necessary to use scopolamine and, in some instances, duboisine. In cases with an increased intra-ocular tension, eserine may be required. For patients who have a sensitivity to eserine or when much local irritation should be avoided, pilocarpine or a combination of pilocarpine and eserine may be used.

It is extremely important to prevent the formation of synechia which may be the forerunner of a secondary glaucoma. A large number of cases have had either a transitory attack of glaucoma or a secondary glaucoma as a result of the uveitis. In any case of uveitis with a transitory stage or secondary glaucoma, especially when there is degeneration

of the pigment of the iris or a low-grade exudative process, the use of local heat in the form of hot compresses and deep heat in the form of diathermy is of benefit to some of these patients. If there is deep-seated inflammation, heat treatment not only makes the patient more comfortable, but also aids the healing process.

The excessive use of tobacco must be restricted, and regulation of the daily bowel and rest habits may be necessary in order to secure the best possible general result. The eyes must be used very guardedly, especially during attacks. No attempt should be made to minimize the seriousness of any form of uveitis. It is one of the most serious diseases encountered in ophthalmology and produces more blindness than all other diseases, including primary glaucoma, and it is frequently the forerunner of secondary glaucoma. If not intensely and directly treated with good judgment, the loss of vision in one or both eyes may be the end result.

## Summary

1. Uveitis usually is due to multiple causes.

2. Foci of infection should be removed in the order of their importance in the etiology of this condition.

3. The general condition of the patient is of prime importance and general measures should be instituted at once to bring the patient to the best state of health possible.

4. Hospitalization may be required in certain cases in which a course of typhoid vaccine therapy or diathermy to the orbit is necessary.

5. Adequate local treatment should be given. During the attack, atropine, eserine, or surgery may be necessary. The use of vaccine, such as old tuberculin or undulant fever vaccine, is necessary in some instances and must be continued over a long period of time.

6. Uveitis is one of the most devastating of all ocular diseases. A guarded prognosis must be given. The best results are obtained only after adequate and aggressive local and general treatment has been carried out.

# The Frank E. Bunts Institute

## DISEASES OF HEART, CIRCULATION, AND KIDNEYS

### Monday, March 24, 1941

| | | |
|---|---|---|
| 9:00 A. M.—12:00 Noon | *PANEL*: The Heart in Relation to General Diseases | A. C. ERNSTENE, M. D. Chairman |
| | 1. A. Syphilis | A. C. ERNSTENE, M. D. |
| | B. Treatment of Cardio-Vascular Syphilis | E. W. NETHERTON, M. D. |
| | 2. A. Heart in Relation to Diseases of the Thyroid | A. C. ERNSTENE, M. D. |
| | B. Atypical Hyperthyroidism | E. P. MCCULLAGH, M. D. |
| | C. Surgery of the Thyroid | R. S. DINSMORE, M. D. |
| | 3. A. Hypertension | R. H. MCDONALD, M. D. |
| | B. Surgical Treatment of Hypertension | GEORGE CRILE, SR., M. D. |
| | QUESTIONS AND ANSWERS | |
| 12:00 Noon— 1:30 P. M. | Lunch | |
| 1:30 P. M.— 2:00 P. M. | The Clinical Diagnosis and Treatment of the Cardiac Arrhythmias | A. C. ERNSTENE, M. D. |
| 2:00 P. M.— 2:45 P. M. | Neurocirculatory Asthenia | E. P. MCCULLAGH, M. D. |
| 2:45 P. M.— 3:30 P. M. | The Diagnosis and Treatment of Coronary Heart Disease | A. C. ERNSTENE, M. D. |
| 3:30 P. M.— 4:30 P. M. | Rheumatic Heart Disease | F. E. BUNTS LECTURE |
| 4:30 P. M.— 5:00 P. M. | Angina Pectoris Due to Rheumatic Heart Disease with Aortic Insufficiency | R. W. SCHNEIDER, M. D. |
| 6:00 P. M. | Dinner | |
| 8:00 P. M. | Frank E. Bunts Lecture | To be announced |

### Tuesday, March 25, 1941

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| 9:00 A. M.— 9:45 A. M. | Embryological and Congenital Abnormalities of the Kidney | W. J. ENGEL, M. D. |
| 9:45 A. M.—10:30 A. M. | Lesions of the Kidney Producing General Symptoms | C. C. HIGGINS, M. D. |
| 10:30 A. M.—11:15 A. M. | Renal Function Tests—Their Clinical Value and Interpretation | R. H. MCDONALD, M. D. |
| 11:15 A. M.—12:00 Noon | The Diagnostic Value of the X-Ray in Lesions of the Kidneys: Methods of Differentiation | B. H. NICHOLS, M. D. |

## Tuesday, March 25, 1941—Cont.

| | | |
|---|---|---|
| 12:00 Noon— 1:30 P. M. | Lunch | |
| 1:30 P. M.— 2:30 P. M. | Surgical Lesions of the Kidney | W. E. LOWER, M. D. |
| 2:30 P. M.— 3:15 P. M. | End Results of Renal Calculi, Including Dietary Regimen | C. C. HIGGINS, M. D. |
| 3:15 P. M.— 4:00 P. M. | Association of Unilateral Kidney Disease with Hypertension—Management | W. J. ENGEL, M. D. |
| 4:00 P. M.— 4:45 P. M. | The Management of the Nephritic Patient | R. H. MCDONALD, M. D. |
| 6:00 P. M. | Dinner | |
| 8:00 P. M. | Clinical X-Ray Conference | |

## Wednesday, March 26, 1940

| | | |
|---|---|---|
| 9:00 A. M.—10:00 A. M. | Diagnosis and Treatment of Peripheral Vascular Disease | W. J. ZEITER, M. D. |
| 10:00 A. M.—10:45 A. M. | The Medical and Surgical Treatment of Varicose Veins | T. E. JONES, M. D. |
| 10:45 A. M.—11:30 A. M. | The Management of the Arteriosclerotic Patient | JOHN TUCKER, M. D. |
| 11:30 A. M.—12:00 Noon | Vascular Lesions of the Head Amenable to Surgical Treatment | W. J. GARDNER, M. D. |
| 12:00 Noon— 1:30 P. M. | Lunch | |
| 2:00 P. M. | Medical Clinics | RUSSELL L. HADEN, M. D. Chairman |

## REGISTRATION BLANK

....., 1941

THE FRANK E. BUNTS INSTITUTE
Cleveland Clinic
Cleveland, Ohio

*Gentlemen:*

Please register me for the course in "Diseases of the Heart, Circulation, and Kidneys" which is to be given on March 24, 25, and 26, 1941.

I am enclosing a check for $5.00, and the remainder of the fee, $5.00, will be paid on registration, March 24.

Name .....

Address .....

.....
Medical School from which graduated.

Note: Checks should be made payable to the Frank E. Bunts Institute and sent to A. D. Ruedemann, M. D., Cleveland Clinic, Cleveland, Ohio.